International Journal of
Molecular Sciences

MDPI

Review

The Role of Karyopherins in Oncopathology

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Abstract

Karyopherins, comprising nuclear import and export receptors, regulate the localisation and activity of proteins and RNA cargoes involved in cell proliferation, survival and stress responses. The oncological consequences of altered karyopherin activity depend on the transported cargo, tumour genotype and cellular conditions. As a result, a karyopherin that supports oncogenic transcription in one setting may preserve tumour suppression in another. This review examines the roles of exportins, importins and bidirectional karyopherins in cancer, relating their cargo-specific functions to tumour growth, treatment resistance and potential biomarker applications. Recent experimental studies associate altered karyopherin activity to oncogenic transcription, metabolic adaptation, DNA repair, RNA processing and treatment resistance. However, individual receptors can also maintain tumour-suppressive functions, and their effects depend on cargo availability and tumour genotype. Karyopherins offer a mechanistically diverse class of oncology targets whose clinical value must be established within defined molecular and disease contexts.

Keywords: karyopherin; exportins; importins; oncology; cancer

1. Introduction

Cancer develops when the mechanisms controlling cell proliferation, differentiation and survival become disrupted. Malignant cells acquire the ability to sustain growth and evade growth-suppressive signals and apoptosis. These changes depend on the abundance, activity and interactions of proteins within cellular signalling pathways.

Protein function also depends on subcellular localisation. Transcription factors, tumour suppressors and DNA repair proteins must reach the appropriate cellular compartment to act. Altered transport between the nucleus and cytoplasm can therefore affect gene expression, cell-cycle checkpoints and responses to stress. In cancer, this distribution may be disturbed by changes in the expression or activity of nucleocytoplasmic transport receptors [1]. Increased activity of the nuclear exporter XPO1/CRM1 can contribute to the nuclear exclusion of tumour suppressors, including p53, FOXO3, p27 and pRb, limiting their nuclear functions. XPO1 recognises leucine-rich nuclear export signals (NESs) and mediates the export of numerous cargo proteins [1,2].

Nucleocytoplasmic transport (NCT) takes place through nuclear pore complexes embedded in the nuclear envelope. Karyopherins mediate much of the regulated transport of proteins and selected RNA cargoes through these pores. The karyopherin-β family includes importins, exportins and bidirectional receptors that transport different cargoes into or out of the nucleus. Their tandem HEAT repeats form a flexible structure that

Academic Editor: Hassan Mubarak Ishqi
Received: 29 October 2026
Revised: 23 November 2026
Accepted: 25 November 2026
Published: 26 November 2026

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accommodates interactions with cargoes, adaptors and nucleoporins. Karyopherin-α proteins are structurally distinct adaptors whose armadillo repeats recognise classical nuclear localisation signals. During classical nuclear import, importin-α binds the cargo and recruits importin-β1 through its N-terminal importin-β-binding domain. Importin-β1 then mediates passage through the pore by interacting with phenylalanine–glycine-rich nucleoporins [3–7].

The compartmentalised Ran GTPase cycle determines the direction of transport (see Figure A1). Representative nuclear import, export, and bidirectional transport pathways involving cancer-associated cargoes are illustrated in Figure A1 (Appendix B). Nuclear RanGTP promotes cargo release from import receptors and the assembly of export receptor–cargo complexes. In the cytoplasm, export complexes disassemble in coordination with GTP hydrolysis, releasing cargo and allowing receptor recycling [7–9].

The effects of altered karyopherin activity in cancer depend on the cargo, tumour genotype and cellular conditions. The same receptor may support tumour growth in one setting and tumour suppression in another. In experimental models of acute myeloid leukaemia, XPO7 has different effects on cell growth according to TP53 status, involving nuclear p53 abundance and NPAT-dependent histone regulation [10]. The clinical efficacy of the XPO1 inhibitor selinexor in multiple myeloma demonstrates that nuclear transport can be targeted therapeutically. Its toxicity, however, remains a limitation, and evidence supporting the targeting of most other karyopherins is predominantly preclinical [11].

This review examines how exportins, importins and bidirectional karyopherins contribute to cancer biology, with a focus on cargo transport, tumour growth and treatment resistance. It also assesses their potential as biomarkers and therapeutic targets, distinguishing expression associations from demonstrated functional dependencies and clinical benefit (see Table A1). The karyopherins discussed, their reported cargoes, associated malignancies and expression-related findings are summarised in Table A1 (Appendix A). Table A2 (Appendix A) summarises the molecular mechanisms and pathways linking these receptors to specific malignancies.

Throughout this review a distinction is maintained between two classes of evidence. Associations between karyopherin expression level and tumour grade, disease stage or survival of patients linked to expression patterns of the protein(s) in clinical material. Thus, the expression level of karyopherins may accompany tumour growth rather than cause it. Mechanistic claims are therefore restricted to studies in which a receptor was depleted, overexpressed or mutated and a defined cargo was shown to change its localisation or activity. Where only correlative evidence is available, this is stated explicitly.

2. Exportins

2.1. Exportin 1/Chromosome Region Maintenance 1 (XPO1 or CRM1)

Under physiological conditions XPO1 is the principal nuclear export receptor of the karyopherin-β family. It recognises short leucine-rich nuclear export signals through a hydrophobic groove formed by HEAT repeats 11 and 12, and releases its cargo into the cytoplasm following RanGTP hydrolysis. Its repertoire extends to several hundred proteins and to multiple RNA classes, including ribosomal subunits, U snRNAs and selected mRNAs and microRNAs, with export of the pre-60S subunit proceeding through the adaptor NMD3. XPO1 therefore contributes directly to ribosome biogenesis and to the spatial separation of signalling intermediates in normal cells. These housekeeping functions explain why XPO1 is essential in non-malignant tissue, and why its pharmacological inhibition carries on-target toxicity, a consideration that recurs throughout the clinical data discussed below.

This is one of the most characterised karyopherins in oncology and the most clinically advanced therapeutic target within the nucleocytoplasmic transport system. XPO1 is

overexpressed at the mRNA and protein level across a wide range of solid and haematological malignancies. Glioblastoma (GBM) is used here as the worked example because the cargo biology has been characterised in most detail in that setting, where XPO1 overexpression has been mechanistically linked to the cytoplasmic accumulation of a broad spectrum of tumour suppressor proteins whose nuclear activity is required for cell cycle arrest, apoptosis, and differentiation [2,12]. These cargos include p53, FOXO3a, phosphorylated retinoblastoma protein (pRb), the CDK inhibitors p21 and p27, and survivin, collectively representing the principal nodes of G1/S checkpoint control and apoptotic competence. For example, in GBM, XPO1-associated cytoplasmic displacement of these proteins can attenuate their nuclear functions, without requiring any change at the genomic level.

The clinical translation of this biology has proceeded through the development of selective inhibitor of nuclear export (SINE) compounds which are reversible inhibitors of XPO1 that block its nuclear export signal (NES) binding groove at Cys528 [2,13]. Selinexor (KPT-330), the first SINE compound approved by the FDA for haematological malignancies, has been evaluated in recurrent GBM. In the uncontrolled phase II KING trial, Lassman et al. [14] demonstrated that selinexor achieved measurable CNS penetrance with intratumoral drug concentrations sufficient for target engagement and showed biological activity including restoration of nuclear tumour suppressor localisation. In the 80 mg weekly arm, five of 30 patients were progression-free at six months, satisfying the prespecified decision rule (Kaplan–Meier estimate, 17.2%); the response rate was 10%. The 30% alternative-hypothesis PFS6 target was not attained [14].

Clinical efficacy is better established in multiple myeloma than in GBM. In the single-arm STORM study, selinexor plus dexamethasone produced a response in 26% of 122 patients with triple-class-refractory myeloma, but the median response duration was 4.4 months [15]. In the randomised phase III BOSTON study after one to three prior therapies, weekly selinexor, bortezomib and dexamethasone prolonged median progression-free survival to 13.93 months versus 9.46 months with bortezomib and dexamethasone (hazard ratio 0.70); grade 3–4 thrombocytopenia was more frequent (39% versus 17%) [11]. The US diffuse large B-cell lymphoma indication was withdrawn on 30 April 2026, while the multiple myeloma indications remain [16]. Clinical use also requires attention to nausea, fatigue, hyponatraemia, infections and dose modification, with antiemetic and hydration support as appropriate. These treatment burdens and the uncontrolled nature of STORM temper extrapolation to other cancers.

An important mechanistic complexity has emerged regarding selinexor in GBM. Tang et al. [17] demonstrated that autophagy modulates GBM cell sensitivity to selinexor-mediated XPO1 inhibition, with GBM cells, notoriously resistant to apoptosis, activating cytoprotective autophagy as an adaptive survival response to nuclear export blockade. This autophagy-mediated resistance mechanism may partially explain the limited single-agent efficacy observed clinically and suggests that combination strategies incorporating autophagy inhibition may enhance SINE compound activity in GBM [17]. Additionally, Mapunda et al. [18] reported that selinexor paradoxically induces MGMT expression via PKA-CREB signalling, potentially contributing to temozolomide resistance, a finding with important implications for combination sequencing strategies. However, besides its clear anti-oncological effect, the haematological toxicity remained a major limitation in clinical settings [18].

The second-generation SINE compound called Eltanexor (KPT-8602) with reduced toxicity effectively reduces viability of glioblastoma and glioblastoma stem-like cells at nanomolar concentrations and sensitises these cells to radiotherapy and temozolomide, addressing the critical challenge of therapy resistance to those drugs [19]. Eltanexor retains XPO1 binding at Cys528 but has lower CNS penetration than selinexor. Its in vitro

activity does not establish adequate drug delivery to intracranial GBM. The combination of XPO1 inhibition with Bcl-2 family antagonism represents a particularly rational strategy in GBM, given the anti-apoptotic excess that characterises these tumours. Zhao et al. [20] tested the E.V.A. regimen (eltanexor, venetoclax, and the Mcl-1 inhibitor A1210477) in combination with conventional chemotherapeutic agents and demonstrated synergistic cytotoxicity in GBM cell lines and primary GBM stem-like cells. The mechanistic rationale is that XPO1 inhibition restores nuclear tumour suppressor-driven pro-apoptotic signalling while Bcl-2/Mcl-1 inhibition simultaneously lowers the apoptotic threshold, overcoming the dual resistance mechanisms that limit monotherapy efficacy [20].

The preclinical compound FR-027 is a reversible covalent XPO1 inhibitor. Its binding conformation has been linked to the absence of XPO1 degradation observed with some other inhibitors [21]. Beyond SINE compounds, Princiotto et al. [22] developed chromenone derivatives as novel CRM1 inhibitors that block nuclear export of oncogenic substrates in a structure- and dose-dependent manner, exhibiting selective cytotoxicity against glioblastoma cell lines and expanding the chemical diversity of available XPO1-targeting agents [22].

In paediatric neuro-oncology, XPO1 inhibition represents a similarly active area of investigation. Green et al. [23] established the recommended phase II dose of selinexor in children with recurrent CNS tumours, and Galinski et al. [24] reviewed the broader therapeutic potential of exportin-1 targeting in childhood cancers. Rallis et al. [25] included XPO1 inhibitors among novel targeted therapies under investigation in early-phase trials for paediatric high-grade glioma. The phase I ADVL1414 study found no objective responses and identified clinically important toxicities; its plasma pharmacokinetics did not demonstrate paediatric intratumoral exposure [23]. Because outcomes differ markedly between medulloblastoma subgroups, from the favourable prognosis of WNT-activated tumours to the poor outcomes of Group 3, future studies in this tumour should be subgroup-stratified to establish whether transport dysregulation is a subgroup-specific vulnerability rather than a pan-tumour phenomenon [25,26].

Taken together, these findings establish karyopherins not merely as transport machinery but as multifunctional regulators of proteostasis, gene expression, and cell division, each of which constitutes a distinct axis of oncogenic vulnerability in tumours.

2.2. Exportin 2/Cellular Apoptosis Susceptibility/Chromosome Segregation 1 Like (XPO2 or CAS or CSE1L)

This protein has three identified and documented functions. First is its canonical function of NCT; it is responsible for recycling in cytoplasm karyopherin alpha family members to reset the cycle of KPNA/B mediated traffic of import in the nucleus of NLS carrying cargos. Second, XPO2 is associated with mitotic spindle and kinetochores that contributes to chromosome segregation. This was first reported by Scherf et al. [27], who demonstrated that the intracellular distribution of CAS resembles that of tubulin in interphase cells and that the protein labels the mitotic spindle in dividing cells. Notably, the same study established that CAS is removed from microtubules by mild detergent treatment and disperses following taxol or vincristine exposure, indicating that it associates with the microtubule network rather than forming an integral part of it. However, a deeper understanding of this association, and of its relationship to the transport function of XPO2, remains enigmatic. The third role is that CAS is involved in modulation of apoptosis. Originally identified as a mediator of apoptosis susceptibility, CSE1L has context-dependent roles; it can promote apoptosis in some settings while supporting cell survival/proliferation in others. It is highly expressed in cancer and regulates invasion and metastasis of cancer cells, being highly related to late cancer stage, high cancer grade, and worse outcomes of patients [28,29]. The recent studies associate it with oral cancer via

MITF regulation [30], gastric cancer where its suppression may enhance the efficacy of the main therapy [31], colon adenocarcinoma where it acts as prognostic biomarker [32]; it is also a pharmaceutical target for various tumours [33].

2.3. Exportin 3/Exportin tRNA (XPO3 or XPOT)

Exportin 3 is the dedicated nuclear export receptor for mature tRNA [34]. It binds tRNA cooperatively with RanGTP and recognises its cargo through conserved structural features of the acceptor and TΨC arms rather than through a linear sequence signal. Of note, this recognition is selective for correctly processed and modified transcripts, so that XPO3 performs a quality-control function that couples tRNA maturation to delivery to the translational machinery [35]. Because the supply of mature tRNA constrains translational capacity, XPO3 activity sits upstream of the elevated protein synthesis that sustains rapid proliferation, which provides a mechanistic rationale for its involvement in cancer that is independent of the expression correlations described below.

The reported associations with malignancy remain largely observational. XPO3 inhibition suppressed breast cancer progression [36], and XPO3 expression has been proposed as a prognostic biomarker in hepatocellular carcinoma [37] and as a candidate therapeutic target in neuroblastoma [38]. The most developed mechanistic account comes from breast cancer, in which XPO3 activity has been linked to PI3K/AKT/mTOR signalling [39,40]. However, whether this reflects a transport-dependent effect on cytoplasmic tRNA availability or an indirect consequence of altered proliferation has not been resolved, and no study has yet tested whether the proliferative effects of XPO3 depletion can be rescued by restoring tRNA supply. Defining the cargo dependence of these phenotypes is therefore the necessary next step before XPO3 can be regarded as a validated target.

2.4. Exportin 5 (XPO5)

It mediates export of micro-RNA precursors (pre-miRNAs), synthetic short hairpin RNAs, double-stranded RNA-binding domain (dsRBD), and double-stranded RNAs [41]. New studies revealed its increasing role in oncogenesis where its upregulation or downregulation are both associated with the cancer onset and progression. Its overexpression has been correlated with the melanoma, colorectal and gastric cancer progressions [42–44]. Also, it is one of the essential part in assembling cancer exosomes that promotes tumorigenesis in distant cells and, as a result, contributing to metastasis of the cancer [45]. Meanwhile, its downregulation due to the XPO5-inactivation gene mutation has been linked to the development of the thyroid and larynx cancers [46,47]. The molecular mechanisms underlining the oncogenic activity of XPO5 is still enigmatic. One of the theories is that alteration in XPO5 expression level or inactivating gene mutations traps miRNA in nucleus as the result leading to pathological change of whole cellular miRNA profile and diminishes miRNA–target inhibition, while restoration of XPO5 functions has tumour-suppressive functions [48,49]. Wen et al. showed that particulate type of the SNP of XPO5 gene leading to XPO5 downregulation correlated with distant metastasis and lymphatic invasion in thyroid cancer. In contrast, other researchers showed that low level of XPO5 due to AC genotype SNP mutation is linked to better therapy response and overall survival in non-small-cell lung and multiple myeloma cancer patients [50,51]. However, AC genotype is also associated with higher risk of oesophageal and renal cancers [52,53]. Additionally, it has been shown that silencing XPO5 effectively suppresses triple-negative breast cancer progression via inhibiting cancer exosome assembly [54]. XPO5 expression can be modulated not only via genetic level by also via post-translational modifications. For example, XPO5 phosphorylation and suppression mediated by ERK related to poor prognosis and high drug resistance in liver cancer patients [55].

2.5. Exportin 6 (XPO6)

Exportin 6 mediates the nuclear export of actin. Notably, it recognises actin in complex with profilin-1 (Pfn-1) rather than actin alone, and this preference is what maintains the low nuclear actin concentration of somatic cells [56]. The distinction matters because nuclear actin is not inert: it participates in chromatin remodelling, in the activity of all three RNA polymerases and in the regulation of MRTF-A, so that XPO6 sets the nuclear availability of a protein with direct transcriptional functions [57]. Loss of XPO6 consequently produces nuclear accumulation of both actin and profilin-1, and the cellular outcome depends on which of the two cargoes predominates in a given setting.

This cargo logic accounts for the opposing roles reported in cancer. Profilin-1 displays anti-oncogenic activity in breast, bladder and pancreatic cancer models, and nuclear profilin-1 represses MYC transcription through its interaction with ENL within the super elongation complex (SEC) [58]. Correspondingly, suppression of XPO6 in breast cancer cells caused nuclear accumulation of profilin-1 and inhibited MYC transcription [58], which places XPO6 in the unusual position of a receptor whose inhibition is predicted to be beneficial through retention of a tumour-suppressive cargo. Whether this holds in tumours in which nuclear actin-dependent transcription predominates remains untested. XPO6 therefore illustrates with particular clarity why the consequences of receptor inhibition cannot be inferred from receptor abundance alone. Beyond oncology, XPO6 has additionally been associated with oogenesis and proposed as a circulating biomarker in major depressive disorder [59–61].

3. Importins

3.1. Karyopherin Alpha 1 & 2 (KPNA1 & KPNA2)

A recent study showed that KPNA1 localised in the nucleolus of the cells and is directly associated with changes in box C/D small nucleolar ribonucleoprotein-related components particularly with DDX21, NOP58, NOP56, and fibrillarin [62]. Meanwhile, other studies directly related each of these components with oncological diseases such as triple-negative breast cancer, hepatocellular carcinoma, leukaemia, colorectal and lung cancer [63–70]. Furthermore, it has been shown that in oesophageal carcinoma tumour-associated macrophages containing circular RNA AP22B1 binds to the transcription factor ESRRA and KPNA1 and translocates in the nucleus, where ESRRA activates MFN2 that creates pro-tumour intracellular environment [71]. Additionally, Wang et al. showed that KPNA1 directly facilitate NSUN2 translocation in the nucleus which is the key event in progression of the bladder cancer [72]. These studies indicate the increasing role of KPNA1 in tumorigenesis and its metastasis, and even suggest it as potential therapeutic target in some of oncological disorders [73].

KPNA2 (importin-α1) is overexpressed at both the mRNA and protein level in GBM relative to normal brain parenchyma. In a seminal immunohistochemical study of 94 primary astrocytomas spanning WHO grades II–IV, Gousias et al. [74] demonstrated that nuclear KPNA2 expression correlated significantly with histological grade ($p < 0.001$), proliferative activity (MIB1 index; $p < 0.001$), and IDH1 mutation status ($p = 0.032$) [74]. Multivariate analysis identified low KPNA2 expression (<5%) as an independent predictor of both overall and progression-free survival, and long-term survival (>5 years) in GBM patients was observed exclusively among those with KPNA2 expression ≤1% [74]. These findings have been corroborated by transcriptomic analyses from TCGA and CGGA cohorts confirming that high KPNA2 expression predicts poor prognosis in glioma patients [75]. These data establish KPNA2 abundance as a prognostic marker in glioma, but they are associational. Because nuclear KPNA2 staining correlates closely with the MIB1 proliferation index within the same cohort, elevated KPNA2 may in part report a high

proliferative fraction rather than drive it. Evidence for a causal contribution comes instead from the functional studies described below, and not from the survival correlations themselves.

The oncogenic consequence of KPNA2 overexpression is cargo-dependent and context-specific. KPNA2 mediates the nuclear import of c-Myc, and Li et al. [76] demonstrated that KPNA2 promotes metabolic reprogramming in GBM through regulation of c-Myc-dependent glycolytic gene transcription, coupling nucleocytoplasmic transport to the Warburg effect [76]. KPNA2 has also been implicated in p53 nuclear localisation under genotoxic stress, illustrating that its consequences cannot be inferred from receptor abundance alone. Lu et al. [77] demonstrated that KPNA2-dependent disruption of TP53 nuclear translocation in GBM cells regulates autophagy and the epithelial-to-mesenchymal-like transition phenotype, linking KPNA2 cargo biology to both invasion and therapy resistance [77].

More recently, El-Sehemy et al. [78] identified a novel KPNA2 cargo axis in GBM stem cells, showing that importin-α transports Norrin to the nucleus to promote Notch signalling and proliferation. Loss of KPNA2 function in patient-derived GBM stem cells shifted Norrin from a nuclear to cytoplasmic distribution and completely abrogated its proliferative and Notch-activating functions [78]. Additionally, the mechanistic relevance of karyopherin overexpression in medulloblastoma is most compelling in the context of Group 3 and Group 4 tumours, in which MYC-family amplification occurs in selected cases, rather than defining either subgroup [79]. KPNA2 mediates the nuclear import of c-Myc and N-Myc; in tumours with amplified *MYC* family genes, KPNA2 overexpression may amplify nuclear accumulation of already-elevated Myc protein, compounding oncogenic transcriptional output. This is mechanistically grounded by the demonstration that KPNA2 regulates c-Myc nuclear localisation and Myc-dependent metabolic reprogramming in glioblastoma [76], though direct experimental validation in medulloblastoma models remains outstanding. Additionally, KPNA2-mediated Hippo/YAP signalling has been implicated in glioma growth and migration, with transcription factor ZNF143 directly binding the KPNA2 promoter to sustain its overexpression [75]. Functional studies support further investigation of KPNA2: silencing of KPNA2 promotes cell-cycle arrest and apoptosis specifically in GBM cells, although these depletion experiments do not establish oncogene addiction or clinical selectivity [80].

3.2. Karyopherin Alpha 3 & 4 (KPNA3 & KPNA4)

Both of these proteins belong to the same subfamily of KPNAs due to the evolutionary closeness and structural identity [7,81]. Therefore, they share cargo proteins that facilitate importing inside the nucleus like RCC1 and RanBP3. However, they have different cargo specificity in cancer; KPNA3 has been reported to promote nuclear accumulation of Xeroderma pigmentosum Group A DNA-repair protein in case of UV-induced damage [82]. This mechanism and protein is crucial in the onset and progression of the skin and hepatocellular cancer [83,84]. Furthermore, its downregulation has been linked to tumorigeneses where its suppression by miR-223 lead to contraction of NF-kB signalling pathway that is the molecular phenotype of chronic lymphocytic leukaemia and mantle cell lymphoma [85].

A distinct and mechanistically better-defined cargo relationship has recently been established for KPNA3. Xu et al. [86] identified KPNA3 as the specific import receptor for NPAT, the scaffold protein that initiates and maintains the histone locus body, a membraneless nuclear compartment governing transcription of the replication-dependent histone genes. KPNA3 recognises the nuclear localisation signal of NPAT, and its depletion reduced nuclear NPAT abundance. Remarkably, the same interaction performs a second function, since anchoring of KPNA3 to the NPAT nuclear localisation signal sterically

blocks the adjacent C-terminal self-interaction facilitator motif through which NPAT self-associates, thereby preventing inappropriate condensation of NPAT in the cytoplasm. KPNA3 therefore determines both where NPAT is located and whether it condenses.

Of note, NPAT is the point at which three karyopherins discussed in this review converge, although by different routes and with different consequences. KPNA3 imports it and restrains its condensation [86], XPO1 exports it and suppresses histone locus body formation by competitively occupying the same self-association sites [87], and XPO7 retains it in the nucleus, which sustains proliferation in TP53-mutated acute myeloid leukaemia [10]. The first two relationships were established in cell-biological systems rather than in cancer models, so a direct contribution of the KPNA3–NPAT axis to tumorigenesis remains to be tested. However, this convergence illustrates the central argument of the present review with unusual clarity, in that the consequence of altering a transport receptor depends on the cargo it handles and on the direction in which it moves it, and a single cargo can connect receptors whose effects on tumour growth are opposite.

KPNA4 has been associated with transportation and regulation of micro-RNAs 181b and 567, RREB1, p53, and hMSH2 under stress and pathological conditions [88–92]. These proteins are one of the key players in the onset and progression of tumorigeneses. Beyond this indirect involvement, an increasing number of studies report that elevated KPNA4 abundance is associated with aggressive disease, metastasis and poorer overall survival in prostate and breast cancer, head and neck squamous cell carcinoma and glioblastoma [88,91–93]. These reports are correlative and do not by themselves establish that KPNA4 drives invasion or metastasis; the evidence for a direct mechanistic contribution comes from the functional experiments described below. Recent studies showed that KPNA4 may play direct mechanistic role in tumorigeneses where its phosphorylation at Ser60 increase its nuclear importing of RREB1 which suppress miRNA-143/145 as the result leading to positive oncogenic feedback loop [93]. Hence, these authors and other studies suggest that targeting of KPNA4 display highly promising therapeutic value [94,95]. This suggestion has been supported by the research conducted in following year by Feng et al., 2021 where authors knockdown KPNA4 in mice as the result inhibit xenograft tumour growth [96].

The molecular mechanism underlying this effect is that KPNA4 knockdown lead to decrease in nuclear level of NF-kB that promotes proliferation of cells and further spread in other tissues. Further studies revealed and supported this findings that increased level of KPNA4 associated with advanced stage of pancreatic ductal adenocarcinoma and mechanistically linked to FAK signalling pathway [97]. Additionally, it has been reported that increased level of KPNA4 not only associated with higher tumour progression and worse survival, but also to drug resistance in cancer patients [98]. Interestingly, a recent paper by Wang et al. elucidated the mechanism of this drug resistance. They showed that hypoxia in hepatocellular carcinoma increases KPNA4, which leads to abnormalities in mitochondrial content and function and, as a result, to a decrease in ROS levels and an increase in drug resistance [99]. Meanwhile, in the same study, authors decreased level of KPNA4 via shRNA that resulted in restored drug sensitivity. Also, they developed oxygen-delivering haemoglobin nanoclusters that reduce hypoxia; when administered to mice, these nanoclusters reduced tumour growth and KPNA4 levels and increased treatment efficacy.

3.3. Karyopherin Alpha 5, 6, & 7 (KPNA5, KPNA6 & KPNA 7)

Cancer-associated alterations have been reported for several importin-α isoforms, although accumulating evidence indicates that their functions are highly dependent on tumour type, expression level and cargo specificity. Importin-α6 (KPNA5) is the most restricted of the conventional importin-α isoforms in its expression, being largely confined to the testis in human tissue, with only low-level cytoplasmic expression elsewhere. Its physiological cargo repertoire is correspondingly poorly characterised and no essential somatic function has been defined, which is worth holding in mind when interpreting the tumour data below. KPNA5 was initially identified as a candidate cancer-associated gene through genome-wide sequencing studies that detected recurrent somatic mutations in breast cancer [100,101]. These included the p.F48L mutation within the importin-β-binding (IBB) domain and the p.L179V and p.R319S mutations within the second and fifth ARM-repeat domains, respectively. However, more recent evidence indicates that KPNA5 should not be considered uniformly oncogenic. A comprehensive genomic and transcriptomic analysis of breast cancer showed significant downregulation of KPNA5 in tumour tissue and identified KPNA5 among nuclear-transport factors whose dysregulation was associated with patient outcome [102]. Thus, the functional significance of the previously identified KPNA5 mutations remains unresolved and cannot by itself be interpreted as evidence of an oncogenic role.

Additional studies increasingly support a tumour-suppressive function for KPNA5 in specific cancer contexts. In pancreatic cancer, a regulatory SNHG6–miR-944–KPNA5 axis was identified in which increased KPNA5 expression suppressed cell proliferation and colony formation and enhanced the response of gemcitabine-resistant PANC-1 cells to gemcitabine. KPNA5 expression was also higher in patients who did not develop gemcitabine resistance than in patients with resistant disease [103]. More direct mechanistic evidence has recently been obtained in ovarian cancer. KPNA5 was significantly downregulated in ovarian tumours, and low KPNA5 expression was associated with advanced disease, lymph-node metastasis and shorter overall survival. Experimental KPNA5 overexpression inhibited proliferation, clonogenic growth, migration and invasion and significantly suppressed xenograft tumour growth in vivo. Mechanistically, KPNA5 recognises nuclear localisation signals in the protein tyrosine phosphatase PTPN4 and promotes its nuclear import, resulting in reduced STAT3 Tyr705 phosphorylation and suppression of downstream STAT3 signalling [104]. These findings provide strong evidence that KPNA5 can act as a cargo-dependent tumour suppressor and may additionally influence chemotherapy response.

Importin-α7 (KPNA6) is broadly expressed in human tissue, with the highest transcript abundance reported in skeletal muscle, brain and testis, and it operates as a conventional importin-α adaptor that binds classical nuclear localisation signals and recruits importin-β1. Its distinct physiological contribution is defined most clearly in early development, since targeted deletion of the murine orthologue yields viable animals whose oocytes nevertheless fail to support zygotic genome activation, so that embryos arrest at the two-cell stage. KPNA6 is therefore not functionally redundant with the other importin-α isoforms despite their overlapping cargo preferences, which is the relevant context for interpreting its comparatively modest alteration frequency in tumours. In cancer, KPNA6 was originally identified as an overexpressed gene in granulocytes from patients with chronic myeloid leukaemia compared with healthy controls [105]. Recurrent haploinsufficiency involving the chromosome 1p region containing KPNA6 was also reported in intravenous leiomyomatosis and related smooth-muscle neoplasms of the uterus [106]. More recent studies have provided additional evidence for cancer-associated dysregulation of KPNA6, although its direct mechanistic contribution to tumorigenesis remains poorly defined. Analysis of 535 lung adenocarcinoma and 59 normal samples showed

significantly increased KPNA6 expression in lung adenocarcinoma and indicated that copy-number amplification of KPNA6 occurred more frequently than deletion [107]. Conversely, a 2024 bioinformatic study of 23 nuclear transport receptors across pan-cancer and head and neck squamous cell carcinoma datasets found genomic alterations of KPNA6 in only approximately 1.9% of the 2691 tumours of the Pan-Cancer Analysis of Whole Genomes consortium, the lowest alteration frequency among the receptors examined [108]. Thus, although transcriptional and copy-number alterations involving KPNA6 have now been documented in several malignancies, there remains considerably less direct experimental evidence for KPNA6 than for several other importin-α isoforms, and specific cancer-promoting or tumour-suppressive KPNA6 cargoes have yet to be clearly established.

Emerging evidence also implicates KPNA7 (Importin-α8) in cancer. Importin-α8 (KPNA7) is the most divergent member of the family. Its physiological expression is essentially confined to the oocyte and the preimplantation embryo, where it acts as a maternal factor required for early cleavage and for zygotic genome activation, and where it engages importin-β1 through a conserved importin-β-binding domain. In cattle, transcript abundance in germinal vesicle oocytes exceeds that of the other importin-α genes by orders of magnitude, and recessive mutations in humans cause preimplantation embryo arrest. Expression falls to very low or undetectable levels in most adult tissues. Its re-expression in tumours is therefore better described as the reactivation of an embryonic transport programme than as the overexpression of a housekeeping receptor, which is precisely what makes it attractive as a therapeutic window. Recent analysis of the KPNA family in lung adenocarcinoma demonstrated significant elevation of KPNA7 expression relative to normal lung tissue. KPNA7 also showed a predominance of copy-number amplification over deletion and an area under the receiver-operating-characteristic curve greater than 0.7 for discrimination between lung adenocarcinoma and normal tissue [107]. In breast cancer datasets, KPNA7 genomic alterations showed significant co-occurrence with TP53 and XPO1 alterations, indicating that KPNA7 abnormalities may occur within broader oncogenic nuclear-transport and tumour-suppressor networks [102].

More recent pan-cancer and functional evidence further supports a tumour-promoting role for KPNA7. A 2026 analysis showed that KPNA7 is overexpressed in multiple human malignancies and that elevated KPNA7 expression is associated with unfavourable survival in selected tumour types. KPNA7 expression was additionally associated with immune-cell infiltration, immunoregulatory molecules, tumour mutational burden, microsatellite instability and anticancer-drug sensitivity. Importantly, functional studies in gastric cancer demonstrated that KPNA7 depletion significantly inhibited cell proliferation, clonogenicity, migration and invasion, increased apoptosis, altered cell-cycle progression and suppressed subcutaneous xenograft tumour growth in nude mice [109]. These results provide direct experimental evidence that KPNA7 can support tumorigenic phenotypes and suggest that KPNA7 may represent a potential therapeutic vulnerability in selected cancers. However, the specific nuclear cargoes and signalling pathways responsible for the tumour-promoting effects observed in gastric cancer remain to be defined.

Collectively, these findings substantially extend earlier observations of importin-α involvement in cancer. They demonstrate that individual importin-α isoforms cannot be classified simply as oncogenic or tumour-suppressive on the basis of mutation frequency or expression level alone. Rather, their contribution to cancer appears to depend on tumour type, genomic context, expression level and, critically, cargo specificity. The KPNA5–PTPN4–STAT3 pathway provides a particularly clear example in which isoform-specific nuclear transport directly suppresses oncogenic signalling [104], whereas recent KPNA7 loss-of-function experiments demonstrate that depletion of another importin-α

isoform can suppress tumour growth. Further identification of tumour-specific importin–cargo interactions will therefore be essential for determining whether individual importin-α proteins can be exploited therapeutically.

3.4. Karyopherin Beta 1 (KPNB1)

KPNB1 or importin-β1 is overexpressed in cancer cells and correlates with indices of proliferative activity, consistent with its dual role as the principal import adaptor for KPNA-bound cargo and as an essential regulator of mitotic fidelity [110,111]. During mitosis, when the nuclear envelope dissolves, KPNB1 is redirected to the vicinity of chromosomes where a localised RanGTP environment, maintained by chromatin-associated RCC1, promotes kinetochore capture and bipolar spindle assembly through the regulated release of spindle assembly checkpoint (SAC) proteins [112]. Cervical cancer cells overexpressing KPNB1 show heightened dependence on this mitotic function; RNA interference-mediated depletion of KPNB1 induces SAC activation, mitotic arrest, and apoptosis preferentially in tumour cells relative to normal glial cells, suggesting a degree of oncogene addiction that may be therapeutically exploitable [110,111].

Recent mechanistic work has substantially extended understanding of KPNB1 in GBM. Li et al. [113] demonstrated that the deubiquitinase USP7 stabilises KPNB1 protein by preventing its proteasomal degradation, and that stabilised KPNB1 promotes GBM progression through nuclear import of the transcription factor YBX1, which in turn upregulates the post-synaptic membrane protein NLGN3 which is a known driver of glioma growth within the neural microenvironment. This USP7–KPNB1–YBX1–NLGN3 axis identifies KPNB1 not merely as a general import factor but as a specific conduit linking the nuclear import machinery to tumour-cell NLGN3 regulation [113]. Furthermore, circular RNA KPNB1 has been shown to be overexpressed in GBM and to promote the malignant phenotypes of glioma stem cells through a positive feedback loop driven by TNF-α/NF-κB signalling [114].

In addition to its mitotic role, KPNB1 mediates the nuclear import of Snail (SNAI1), a master regulator of epithelial-to-mesenchymal transition that promotes GBM invasion, a phenotype that is refractory to current therapies and contributes to the near-universal pattern of local recurrence. Notably, Bourmeau et al. [115] recently demonstrated that proneural–mesenchymal hybrid GBM cells, a therapy-resistant subpopulation induced by conventional treatment, are specifically dependent on nuclear import for their survival. This finding positions the nuclear import machinery, including KPNB1, as a vulnerability specific to the adaptive plasticity that drives treatment failure in GBM [115].

3.5. Transportin 1, 2 & 3 (TNPO1, TNPO 2, & TNPO3)

TNPO1 (also known as karyopherin-β2) is one of the most interesting karyopherins, as it has been linked to a wide range of diseases. It recognises cargo mainly through proline-tyrosine nuclear localisation signals (PY-NLSs), the best-characterised class of TNPO1 substrates, although many cargoes carry signals that do not resemble the archetypal PY-NLS [116]. Beyond import, TNPO1 has moonlighting functions, including roles in spindle assembly and in nuclear envelope and pore assembly during mitosis [117]. In neurodegeneration, TNPO1 has been shown to suppress phase separation of the aggregation-prone proteins FUS and TDP-43 and to help maintain their nuclear–cytoplasmic distribution [118–121].

A growing number of studies also point to a role for TNPO1 in cancer. In a serum study of cervical and oesophageal cancer patients, TNPO1 and IPO5 were the best-performing individual markers among the nuclear transport proteins tested, and a seven-protein panel gave AUCs of 0.944 for cervical and 0.963 for oesophageal cancer [122]. Because the panel also included CAS/CSE1L and other karyopherins, this is a family-wide

signal, and TNPO1 is best seen as one component of a panel rather than a standalone marker.

Mechanistic work shows that TNPO1 imports oncogenic cargo. ARID1A is frequently lost in gynaecological cancers, e.g., in about 46% of ovarian clear cell carcinomas [123,124]. ARID1A-deficient cells depend on its paralogue ARID1B; ARID1B was the top gene preferentially required for the growth of ARID1A-mutant cancer cell lines, and its loss destabilises the SWI/SNF complex [125]. B. Yang et al. [124] reported that TNPO1 is upregulated in ARID1A-deficient gynaecological cancer cells, that this is associated with poor prognosis, and that TNPO1 interacts directly with ARID1B and promotes its nuclear import. This import supports proliferation and tumour growth in these cells. In cervical cancer, TNPO1 also imports FUBP1, which is upregulated and linked to poor prognosis, and whose nuclear localisation regulates expression of the immune checkpoint NRP1, linking TNPO1 to tumour immune evasion [126].

However, TNPO1 does not import only oncogenic cargo. It is also the primary importer of the tumour suppressor BAP1, which it recognises through an atypical C-terminal PY-NLS [127]. TNPO1 binding dissociates BAP1 dimers and shields the ubiquitination sites flanking the PY-NLS, counteracting UBE2O, which retains BAP1 in the cytosol. The effect of altered TNPO1 activity in each tumour may therefore depend on which cargo dominates, and TNPO1 inhibition would not necessarily be uniformly anti-tumorigenic. Most evidence so far comes from cargo-by-cargo studies in cell lines, and a systematic picture of TNPO1's contribution across cancers has yet to be established.

TNPO2 (transportin-2 or importin-3) and TNPO3 (transportin-SR2 or importin-12) remain less well characterised in cancer than TNPO1, although both have functional evidence supporting roles in cancer cells. TNPO2 is a close paralogue of TNPO1, and their cargo specificities overlap; both recognise the M9 signal of hnRNP A1 which is involved in regulating alternative splicing, and mediate nuclear import of HuR which is involved in cell survival via regulating mRNA stability and translation [128,129]. TNPO3 primarily imports SR-rich proteins involved in RNA processing, although its recognition mechanisms extend beyond phosphorylated SR domains.

The direct evidence linking TNPO2 to tumorigenesis comes from 2019 research on gastric cancer [130]. DYNC1I1 increases TNPO2 expression through SP1-dependent promoter activation involving P300 and histone acetylation. TNPO2 depletion reduced cell proliferation, induced G1 arrest, increased p21 and enhanced apoptosis, whereas overexpression promoted proliferation and suppressed apoptosis. High TNPO2 expression was associated with poorer survival of cancer patients. The authors proposed p21 as a possible mediator but did not establish the responsible transport cargo. Interestingly, HuR localisation was unchanged following TNPO2 depletion [130].

Meanwhile, in another study on HeLa cells, TNPO2 depletion increased cytoplasmic HuR accumulation and enhanced staurosporine-induced apoptosis, linking HuR trafficking to the response to apoptotic stress [131]. In HeLa and MCF-7 models, TNPO2 bound oestradiol-activated ERα through PY motifs and competed with importin-α, favouring cytoplasmic retention rather than nuclear import. TNPO2 depletion increased nuclear ERα and reduced oestradiol-induced AKT phosphorylation in MCF-7 cells [132]. These findings support context-dependent functions of TNPO2, but neither study established an effect on tumour growth in vivo.

Clinical observations extend these functional findings. TNPO2 protein was elevated in bladder cancer tissues and patient urine, identifying it as a candidate non-invasive biomarker [133]. Transcriptomic analysis also reported increased TNPO2 expression in head and neck squamous cell carcinoma [108]. These associations broaden its potential cancer relevance but do not establish causality or clinical utility.

TNPO3 recognises phosphorylated SR domains, with structural studies defining its interaction with the R-pS-R-pS-R motif of SRSF1 [134]. Its cargo repertoire also includes CPSF6 and CIRBP. CIRBP uses a noncanonical RSY-NLS whose recognition does not require phosphorylation. In contrast, phosphorylation inhibits TNPO3 binding [135–137]. TNPO3 additionally interacts with EBF1 and supports B-cell programming under antagonistic Notch signalling, but this interaction is dispensable for EBF1 nuclear localisation and should therefore be distinguished from cargo import [138].

Direct evidence connects TNPO3-mediated transport to colon cancer cell proliferation. In HCT-116 and SW480 cells, TNPO3 silencing reduced nuclear SRSF1, attenuated the SRSF1-driven shift towards the pro-oncogenic MKNK2b splice isoform, and reduced proliferation and colony formation. This links a defined TNPO3 cargo to a cancer-associated phenotype, although direct in vivo validation of TNPO3 targeting remains lacking in that study [139]. Separately, a mutant TNPO-3-derived neoepitope elicited tumour-specific immunogenic CD8 responses and tumour protection in a mouse fibrosarcoma model, establishing an antigenic role without demonstrating an oncogenic transport mechanism [140].

Overall, TNPO2 and TNPO3 have limited but direct functional evidence in different cancer models. TNPO2 supports gastric cancer cell proliferation and regulates HuR-dependent apoptosis and ERα signalling in distinct contexts, whereas TNPO3 supports SRSF1-dependent splicing and proliferation in colon cancer cells. Their relevance across tumour types and suitability as therapeutic targets remain unresolved. Overlapping cargo recognition may permit compensation between transport receptors, but this requires testing in individual cancer models.

3.6. Importins 4, 5, 7, 8, 9 & 11 (IPO4, IPO5, IPO7, IPO8, IPO9 & IPO11)

These transport diverse chromatin-associated proteins, RNA-binding proteins and signalling regulators. Proteomic analysis of 12 importin pathways revealed both distinct and overlapping cargo repertoires [141]. Their cancer-related functions are supported by individual cargo–tumour mechanisms, although the extent to which these mechanisms generalise across malignancies remains uncertain.

IPO4 imports histones H3–H4 in complex with ASF1. Structural analysis showed that it primarily recognises the folded histone surface rather than the H3 N-terminal tail, supporting a combined transport and chaperone function [142]. Interestingly, IPO4 was overexpressed in gastric cancer, and its depletion reduced proliferation and migration, although the responsible cargo was not identified [143]. A clearer mechanism emerged in cervical cancer where IPO4 promotes NLS-dependent nuclear import of CEBPD, which activates PRKDC transcription and DNA-PKcs-dependent repair of DNA. IPO4 depletion increased cisplatin sensitivity, linking nuclear transport directly to chemotherapy resistance [144]. The same IPO4–CEBPD–PRKDC pathway was subsequently implicated in hypoxic bladder cancer, where IGF2BP2 stabilises IPO4 mRNA [145]. Other cancer-relevant cargoes include SOX2 in ovarian cancer, RNF180-mediated IPO4 ubiquitination impaired SOX2 nuclear localisation and reduced malignant behaviour [146]. These studies support IPO4 as one of the key regulator of tumour growth and treatment resistance, with CEBPD-dependent DNA repair providing the most consistent mechanism across tumour types.

IPO5 imports several biosynthetic and signalling proteins, including BMP receptor-regulated SMADs [147]. Its best-defined cancer mechanism involves RASAL2 in colorectal cancer. IPO5 binds the RASAL2 NLS and promotes its nuclear accumulation, reducing its cytoplasmic RAS-inhibitory activity and thereby enhancing RAS signalling. IPO5 depletion suppressed malignant phenotypes and xenograft growth, while NLS-mutant experiments connected these effects to RASAL2 transport [148]. Thus, nuclear import can

promote tumour growth by removing an inhibitor from its functional compartment. IPO5 depletion also reduced oesophageal tumour growth and EMT-associated changes, although the relevant cargo was not established [149]. Goyazensolide was identified as a covalent IPO5-binding compound that inhibits transport activity and reduces nuclear RASAL2, providing an experimental basis for pharmacological targeting [150]. Separately, elevated serum IPO5 was reported in cervical and oesophageal cancer, supporting investigation as a circulating biomarker rather than establishing a transport mechanism [122].

IPO7 has a broad cargo profile and several experimentally supported cancer mechanisms. In glioblastoma, FOXM1 increases IPO7 expression and thereby promotes GLI1 nuclear localisation [151]. In pancreatic cancer, cingulin stabilises IPO7 mRNA and enhances nuclear accumulation of phosphorylated ERK, linking receptor abundance to oncogenic MAPK signalling [152]. In cervical cancer, IPO7-mediated GTF2I import was associated with PI3K–AKT–mTOR activation and tumour growth [153]. A subsequent study identified MSI2 as an IPO7 cargo whose nuclear import and stabilisation support MYC-associated glycolytic reprogramming [154]. In AR-positive breast cancer models, IPO7 promotes nuclear transport of an AR–USP22 complex. Its depletion inhibited proliferation and increased responsiveness to enzalutamide [155].

IPO7-dependent transport also responds to the cellular environment. YAP is a dominant IPO7 cargo that influences transport of other substrates [156]. In nasopharyngeal carcinoma, circRILPL1 binds IPO7 and facilitates YAP nuclear translocation, promoting transcription of cytoskeletal regulators [157]. Under hypoxia in hepatocellular carcinoma, IPO7 imports SLC25A10 isoform 3, which cooperates with CEBPB to induce the anti-apoptotic gene BCL2A1. Disrupting the cargo–IPO7 interaction increased responsiveness to etoposide in mouse tumour models [158]. These findings suggest that IPO7 dependence is determined by cargo availability and signalling state as well as receptor abundance.

IPO8 connects nuclear transport to metabolic adaptation and RNA regulation. In pancreatic cancer, IPO8 supports nuclear localisation of MiT/TFE transcription factors, particularly TFE3, sustaining an autophagy–lysosome programme that supports tumour metabolism. Combined IPO7/IPO8 depletion affected other MiT/TFE family members, indicating overlapping transport requirements [159]. IPO8 also directly imports eIF4E which is involved facilitating export of mRNA out of nucleus and initiating protein synthesis in cytoplasm [160]. Its depletion reduced nuclear eIF4E, eIF4E-dependent mRNA export and invasion, whereas overexpression increased foci formation in an eIF4E-dependent manner. Elevated IPO8 and altered eIF4E localisation were also observed in AML patient samples [160]. In triple-negative breast cancer, IPO8 facilitates nuclear entry of miR-551b-3p through an AGO1-associated complex. Nuclear miR-551b-3p activates STAT3 transcription and an oncostatin signalling programme associated with tumour progression [161]. IPO8 therefore has direct cancer-related functions involving both protein cargoes and RNA-containing complexes.

IPO9 imports nuclear actin and acts as an importer and chaperone for H2A–H2B, recognising the folded histone core [162,163]. Its relation to cancer extends beyond these housekeeping cargoes. In head and neck cancer, let-7 represses IPO9 and limits ARID3A nuclear localisation, affecting an ARID3B-containing chromatin-regulatory complex and stemness-associated transcription [164]. In T-cell acute lymphoblastic leukaemia, cyclin D3/CDK6 promotes PFKP dimerisation and exposes an NLS recognised by IPO9. Nuclear PFKP increases MYC-dependent CXCR4 expression and leukaemic infiltration. IPO9 depletion reduced nuclear PFKP without changing its total abundance [165].

Recent ovarian cancer experiments linked IPO9 to suppression of HMOX1-dependent ferroptosis and showed reduced tumour growth following IPO9 depletion, although the responsible transport mechanism remains unresolved [166]. Conversely, IPO9

depletion protected MCF-7 cells from apoptosis induced by alliin plus paclitaxel, alongside reduced nuclear/perinuclear F-actin [167]. IPO9 inhibition therefore cannot be assumed to enhance treatment-induced cell death in every setting. Structural identification of ETS domains as IPO9-recognised nuclear localisation signals further expands its potential cancer-relevant cargo repertoire, but dependence of ETS-driven tumours on this transport route remains to be established [168].

IPO11 provides particularly clear evidence that the same receptor can support opposing cancer functions. IPO11 transports PTEN and the ubiquitin-conjugating enzyme UBE2E1, protecting PTEN from cytoplasmic degradation. IPO11 loss caused PTEN depletion, lung adenocarcinoma and prostate neoplasia in mice, establishing a tumour-suppressive role [169]. Conversely, IPO11 supports β-catenin nuclear accumulation and transcription in a subset of APC-mutant colorectal cancers. Its knockout reduced colony formation and patient-derived organoid proliferation [170]. In AML, IPO11 imports BZW1/2, and its depletion reduced growth and leukaemic stem-cell engraftment while promoting differentiation [171]. More recently, IPO11-dependent TRAF2 nuclear translocation was implicated in KIF26B-driven bladder cancer progression [172].

IPO11 also imports RPRM following irradiation. Nuclear RPRM promotes ATM export and degradation, impairing DNA repair and increasing radiosensitivity [173]. Thus, IPO11 activity can preserve tumour suppression, sustain oncogenic transcription or facilitate treatment-induced damage, depending on the cargo. PTEN status and dependence on β-catenin or BZW1/2 are plausible determinants of the response to IPO11 inhibition, but their relative contributions require testing within the same tumour models.

Collectively, these receptors have experimentally supported roles in cancer, although most mechanisms remain defined in particular tumour models. Their effects depend on cargo localisation, stability and function, making receptor expression alone an incomplete measure of transport dependence. Cargo-specific disruption may offer greater selectivity than broad receptor inhibition, particularly where the same importin supports both tumour-promoting and protective pathways.

4. Bidirectional Transporters

4.1. Exportin 4 (XPO4)

This protein is a bidirectional karyopherin that exports eIF5A and SMAD3 and imports SOX2 and SRY [174–176]. Structural analysis showed that it recognises the folded surface and hypusine-containing region of eIF5A, linking cargo modification to export recognition [177]. Its tumour-suppressive role was established in a liver cancer RNAi screen, where XPO4 depletion promoted tumour formation and nuclear accumulation of eIF5A and SMAD3. Restoring XPO4 suppressed growth of XPO4-deficient cells, while eIF5A2 depletion impaired their proliferation, identifying a cancer-relevant cargo dependency [178]. Reduced XPO4 expression was subsequently associated with poor survival in a human HCC cohort [179]. A further mechanism involves PKM2: SIRT6-mediated deacetylation at K433 enables XPO4-dependent nuclear export, restricting its nuclear oncogenic activities [180].

However, XPO4 can also support treatment resistance. In HER2-positive breast cancer, increased XPO4 promotes cytoplasmic redistribution of circ-PPID, reducing its interaction with nuclear NAT10 and permitting NAT10-dependent stabilisation of HER2 mRNA, thereby supporting trastuzumab resistance [181]. In castration-resistant prostate cancer cells, XPO4 knockout increased enzalutamide sensitivity, although the responsible cargo remains unknown [182]. Functional genomic screening also identified XPO4 as a preferential dependency in multiple myeloma [183].

XPO4 additionally supports export of a subset of circular RNAs. Its deficiency causes nuclear RNA accumulation, R-loop formation and DNA damage, suggesting a possible

contribution to genome maintenance, although a causal link to tumourigenesis through this mechanism remains untested [184].

Recent studies extend the association of XPO4 with cancer, although much of the evidence remains observational. Uveal melanoma GWAS meta-analyses identified a susceptibility locus encompassing XPO4, but substantial heterogeneity between cohorts and regulatory associations with several neighbouring genes prevent assignment of the effect specifically to XPO4 [185,186]. In colon adenocarcinoma, database analysis linked elevated XPO4 mRNA to advanced stage and poorer overall survival, whereas higher expression was associated with favourable prognosis in clear-cell renal cell carcinoma [32,187]. These findings indicate tumour-specific associations but do not establish the underlying transport mechanisms. A recent study in cervical cancer cells further suggested that TPR-mediated circRNA export can operate independently of XPO4, indicating that alternative export routes may influence the consequences of XPO4 loss [188]. Collectively, XPO4 has experimentally supported tumour-suppressive and treatment-resistance functions. Its effects depend on the transported cargo, disease, and cellular context, so broad inhibition cannot be assumed to be beneficial across cancers.

4.2. Exportin 7 (XPO7)

Aksu et al. [3] showed that XPO7 is a bidirectional transport receptor; reported export cargoes include 14-3-3, p50RhoGAP and STRAD [189,190]. It has been reported that elevated levels of XPO7 is associated with poor overall survival in high grade epithelial ovarian cancer patients and small intestinal adenocarcinoma [191,192]. Furthermore, point mutation where residue Asp237 of XPO7 is mutated to asparagine (p.D237N) was identified in oligodendrogliomas tumour samples [193].

Functional studies demonstrated context-dependent effect of XPO7 in cancer. It has been shown that depletion of XPO7 lead to tumour formation in an oncogenic Nras-driven mouse model and its loss associated with poorer prostate cancer outcomes [194]. The authors link this effect with the disruption of TCF3 abundance and p21-dependent senescence in cells which maintained by XPO7. Meanwhile, another study demonstrated that elevated levels of XPO7 promotes proliferation, invasion, and epithelial–mesenchymal transition in prostate cancer models whereas its knockdown reduced xenograft growth [195]. Opposing effects have likewise been demonstrated in acute myeloid leukaemia (AML). Using genome-wide CRISPR/Cas9 dropout screens in isogenic Trp53-wild-type and Trp53-knockout AML models, Semba et al. [10] demonstrated that XPO7 regulates the nuclear abundance of p53 in TP53-wild-type AML, where its depletion reduced nuclear p53 and the expression of p53 target genes, consistent with a tumour-suppressive role. It should be emphasised that p53 has not been established as a direct transport substrate of XPO7. The experimentally supported export cargoes remain 14-3-3, p50RhoGAP and STRAD, and the change in nuclear p53 abundance may therefore be indirect. In TP53-mutated AML the same study demonstrated the opposite effect, in which XPO7 sustains proliferation by retaining NPAT, which is a regulator of replication-dependent histone transcription, within the nucleus. Here the evidence for a direct relationship is stronger, since NPAT was recovered as an XPO7-interacting protein by immunoprecipitation and mass spectrometry and shifted towards a cytoplasmic distribution upon XPO7 depletion. NPAT depletion induced genome-wide histone loss and replication catastrophe, particularly in p53-deficient cells. Taken together, these findings establish XPO7 as a context-dependent regulator of tumour growth whose effect varies with tumour type and genetic background.

The two prostate cancer studies reach opposite conclusions and the reasons remain unresolved, although several methodological differences are likely to contribute. Innes et al. [194] approached XPO7 as a senescence regulator identified in a CRISPR screen and

assessed loss of function, reporting that XPO7 depletion disrupts TCF3 abundance and p21-dependent senescence; their in vivo evidence derives from an oncogenic Nras-driven mouse model rather than from prostate tissue. Lin et al. [195] instead assessed gain of function in established prostate cancer cell lines and xenografts, and reported that elevated XPO7 upregulates TCF3 and promotes proliferation, invasion and epithelial-to-mesenchymal transition. The direction of manipulation therefore differs, the models differ, and, remarkably, both studies converge on TCF3 while assigning it opposite consequences. A further consideration is disease stage, since senescence-based tumour suppression is most relevant to early lesions whereas the proliferative phenotype was examined in established tumours. Neither study stratified by molecular subtype and neither established TCF3 as a direct XPO7 cargo. Resolving this discrepancy will require side-by-side comparison of loss and gain of function in the same prostate models, with stage and subtype defined, and with cargo binding tested directly.

4.3. Importin 13 (IPO13)

IPO13 is a bidirectional karyopherin that imports UBC9 and the MAGOH–RBM8A/Y14 complex and exports eIF1A [196]. Structural studies reveal distinct modes of cargo recognition, while proteomic screening suggests a broader cargo repertoire [197–199]. Early evidence in cancer was observational: IPO13 expression was elevated in endometrial carcinoma relative to secretory-phase endometrium, although it also increased in normal proliferative-phase endometrium [200]. Subsequent studies have linked specific IPO13 cargoes to tumour growth and treatment response.

In non-small-cell lung cancer, IPO13 imports RFPL3 through an NLS within its C-terminal B30.2 domain. IPO13 depletion reduced nuclear RFPL3, its occupancy at the hTERT promoter and hTERT expression, and suppressed growth in culture and xenografts [201]. In melanoma, monomeric α-tubulin stabilises c-Jun and facilitates its interaction with IPO13, supporting nuclear import and AP-1 activity [202]. A genetically defined dependency occurs in cancers with hemizygous MAGOH deletion associated with chromosome 1p loss. These cells depend on MAGOHB and IPO13-mediated nuclear transport. IPO13 depletion disrupted MAGOH/MAGOHB localisation and nonsense-mediated mRNA decay and inhibited tumour growth; MAGOH reconstitution rescued the dependency [203].

Two studies published in 2025 connect IPO13 to chemotherapy response. In triple-negative breast cancer, RNF31-mediated linear ubiquitination promotes IPO13-dependent import of ALYREF during paclitaxel treatment. ALYREF import normally involves KPNA2/KPNB1, indicating that treatment changes receptor dependence. Nuclear ALYREF supports export of TUBB3, STMN1 and TAU mRNAs, and IPO13 depletion sensitised resistant cells and suppressed xenograft growth during treatment [204]. In pancreatic ductal adenocarcinoma, the circular RNA cCCT2 binds IPO13 and interferes with UBC9 nuclear import. This reduces SLX4 SUMOylation, stability and condensate formation, impairing DNA repair and enhancing chemotherapy-induced senescence. IPO13 or UBC9 overexpression rescued downstream molecular effects [205].

IPO13 can also support cell death. Following genotoxic stress, CK2α-dependent phosphorylation promotes IPO13-mediated import of PDCD5, facilitating HDAC3 degradation and p53 activation [206]. In HeLa cells, IPO13 imports nuclear clusterin and exports KU70. Under oxidative stress, clusterin import persists whereas KU70 export is impaired; IPO13 depletion reduces nuclear clusterin accumulation and protects against apoptosis [207]. A 2026 study additionally found that IPO13 overexpression helped maintain nuclear Ran during oxidative stress, supporting a role in preserving transport organisation without establishing a tumour-promoting effect [208].

Recent work also extends IPO13's export functions. In vascular smooth muscle cells, oxidative stress promotes IPO13-dependent cytoplasmic translocation of SIRT6, which deacetylates ENO3 and enhances glycolysis [209]. Whether this pathway operates in cancer remains unknown.

Together, these studies identify IPO13 as a context-dependent regulator of tumour growth and treatment response, with the strongest cancer evidence involving nuclear import. MAGOH loss creates a defined vulnerability, while ALYREF and UBC9 connect cargo transport to drug resistance and DNA repair. However, IPO13 also transports pro-apoptotic proteins. Its therapeutic relevance therefore depends on the cargo, tumour genotype and treatment conditions, rather than IPO13 abundance alone.

5. Conclusions

Karyopherins connect nucleocytoplasmic transport to the molecular processes that govern tumour growth and treatment response. The studies reviewed here link individual receptors to oncogenic transcription, metabolic adaptation, DNA repair, RNA processing and apoptosis. Their activities also extend to protein stability, histone handling and mitotic regulation. Although altered karyopherin expression frequently correlates with tumour aggressiveness or patient outcome, these associations alone do not establish the responsible mechanism or demonstrate a therapeutic dependency.

A central finding is that karyopherin function cannot be classified as uniformly tumour-promoting or tumour-suppressive. IPO11 preserves PTEN stability but also supports β-catenin-dependent growth in selected colorectal cancers. Similarly, XPO7 has opposing effects in AML according to TP53 status, while XPO4 suppresses liver tumour formation yet contributes to treatment resistance in other settings. These observations indicate that receptor abundance must be interpreted alongside cargo function, tumour genotype and treatment conditions. They also caution against assuming that inhibition of a receptor will reproduce the benefits observed in another cancer model.

Clinical translation remains most advanced for XPO1 inhibition. Selinexor-containing regimens have demonstrated efficacy in multiple myeloma, whereas activity in glioblastoma and paediatric solid or CNS tumours has been more limited. Toxicity, tissue exposure and adaptive resistance constrain its broader application. For other karyopherins, genetic depletion and experimental inhibitors provide evidence of therapeutic potential, but clinical efficacy and selectivity remain unestablished. Likewise, tissue and circulating biomarker findings require validation before they can guide patient management.

Three obstacles currently limit translation. The first is interpretive, most clinical evidence linking karyopherins to cancer rests on expression correlations in retrospective cohorts, which cannot distinguish a receptor that drives disease from one whose abundance merely tracks proliferation. The second is pharmacological, karyopherins are essential in normal cells, and the toxicity profile of selinexor illustrates the narrow therapeutic window that follows from inhibiting an entire receptor rather than a disease-specific transport event. The third is conceptual, a single receptor may carry both oncogenic and tumour-suppressive cargoes within the same tumour, so the net effect of its inhibition cannot be predicted from receptor abundance and may itself change during treatment.

Several directions follow from these limitations. Cargo-selective disruption, in which the interaction between a receptor and a single pathogenic cargo is blocked while its remaining transport functions are preserved, offers a route around the toxicity of global receptor inhibition, although no such agent has yet reached clinical evaluation. Genetically defined vulnerabilities provide a second route, since TNPO1 dependence in ARID1A-deficient cancers and IPO13 dependence following MAGOH loss both identify patient populations by genotype rather than by expression level. A third requirement is methodological, studies should report cargo localisation alongside receptor abundance,

stratify by molecular subtype, and compare loss and gain of function within the same model, since the opposing findings for XPO7 in prostate cancer illustrate how readily conclusions diverge when these conditions are not met. Finally, whether receptor dependence is itself altered by treatment deserves systematic attention, given that nuclear import becomes a vulnerability in therapy-induced proneural–mesenchymal glioblastoma cells and that the receptor used for ALYREF import changes during paclitaxel exposure.

Karyopherins therefore represent a mechanistically diverse group of candidate targets rather than a single therapeutic strategy. Their clinical value will be established for individual receptor–cargo pairs in defined molecular contexts, and not for the family as a whole.

Author Contributions: Conceptualization, D.S. (Daulet Sharipov) and D.S. (Dos Sarbassov); investigation, D.S. (Daulet Sharipov); writing, original draft preparation, D.S. (Daulet Sharipov); writing, review and editing, D.S. (Daulet Sharipov) and D.S. (Dos Sarbassov); visualization, D.S. (Daulet Sharipov); supervision, D.S. (Dos Sarbassov). All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. BR24993023) and Nazarbayev University CRP (211123CRP1608).

Data Availability Statement: No new data were created or analysed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this review:

AGO1	Argonaute 1
AKT	Protein kinase B
ALYREF	Aly/REF export factor
AML	Acute myeloid leukaemia
AP-1	Activator protein 1
APC	Adenomatous polyposis coli protein
AR	Androgen receptor
ARID1A/ARID1B	AT-rich interaction domain-containing proteins 1A and 1B
ARID3A/ARID3B	AT-rich interaction domain-containing proteins 3A and 3B
ARM	Armadillo repeat
ASF1	Anti-silencing function 1 histone chaperone
ATM	Ataxia-telangiectasia mutated kinase
AUC	Area under the receiver operating characteristic curve
BAP1	BRCA1-associated protein 1
BCL2A1	BCL2-related protein A1
Bcl-2	B-cell lymphoma 2 protein
BMP	Bone morphogenetic protein
BOSTON	Phase III trial of selinexor, bortezomib and dexamethasone versus bortezomib and dexamethasone in multiple myeloma
BZW1/2	Basic leucine zipper and W2 domain-containing proteins 1 and 2
CAS	Cellular apoptosis susceptibility protein; alternative name for CSE1L/XPO2
cCCT2	Circular RNA derived from the chaperonin-containing TCP1 subunit 2 gene
CD8	Cluster of differentiation 8
CDK	Cyclin-dependent kinase
CDK6	Cyclin-dependent kinase 6
CEBPB	CCAAT/enhancer-binding protein β

CEBPD	CCAAT/enhancer-binding protein δ
CGGA	Chinese Glioma Genome Atlas
CIRBP	Cold-inducible RNA-binding protein
circ-PPID	Circular RNA derived from the peptidylprolyl isomerase D gene
circRILPL1	Circular RNA derived from the RILP-like 1 gene
circRNA	Circular RNA
CK2α	Casein kinase 2 catalytic subunit α
CML	Chronic myeloid leukaemia
CNS	Central nervous system
CPSF6	Cleavage and polyadenylation specificity factor subunit 6
CREB	Cyclic AMP response element-binding protein
CRM1	Chromosome region maintenance 1; alternative name for XPO1
CSE1L	Chromosome segregation 1-like protein; also known as CAS or XPO2
CXCR4	C-X-C motif chemokine receptor 4
DDX21	DEAD-box helicase 21
DNA	Deoxyribonucleic acid
DNA-PKcs	DNA-dependent protein kinase catalytic subunit
dsRBD	Double-stranded RNA-binding domain
dsRNA	Double-stranded RNA
DYNC1I1	Dynein cytoplasmic 1 intermediate chain 1
E.V.A.	Eltanexor, venetoclax and A1210477 combination
EBF1	Early B-cell factor 1
eIF1A	Eukaryotic translation initiation factor 1A
eIF4E	Eukaryotic translation initiation factor 4E
eIF5A	Eukaryotic translation initiation factor 5A
eIF5A2	Eukaryotic translation initiation factor 5A2
EMT	Epithelial-to-mesenchymal transition
ENL	Eleven-nineteen leukaemia protein; also known as MLLT1
ENO3	Enolase 3
ERα	Oestrogen receptor α
ERK	Extracellular signal-regulated kinase
ESRRA	Oestrogen-related receptor α
ETS	E26 transformation-specific transcription factor family
F-actin	Filamentous actin
FAK	Focal adhesion kinase
FDA	US Food and Drug Administration
FOXM1	Forkhead box M1
FOXO2/FOXO3a	Alternative names for forkhead box O3 (FOXO3)
FUBP1	Far upstream element-binding protein 1
FUS	Fused in sarcoma
GBM	Glioblastoma
GLI1	GLI family zinc finger 1
GTF2I	General transcription factor IIi
GTP	Guanosine triphosphate
GTPase	Guanosine triphosphatase
GWAS	Genome-wide association study
H2A/H2B/H3/H4	Histones H2A, H2B, H3 and H4
HCC	Hepatocellular carcinoma
HDAC3	Histone deacetylase 3
HEAT	Huntingtin, elongation factor 3, the PR65/A subunit of protein phosphatase 2A and target of rapamycin
HER2	Human epidermal growth factor receptor 2
HGNC	HUGO Gene Nomenclature Committee
HMOX1	Haem oxygenase 1
hMSH2	Human MutS homologue 2

hnRNP A1	Heterogeneous nuclear ribonucleoprotein A1
hTERT	Human telomerase reverse transcriptase
HUGO	Human Genome Organisation
HuR	Human antigen R; also known as ELAVL1
IBB	Importin-β-binding domain
ID	Identifier
IDH1	Isocitrate dehydrogenase 1
IGF2BP2	Insulin-like growth factor 2 mRNA-binding protein 2
IPO4	Importin 4
IPO5	Importin 5
IPO7	Importin 7
IPO8	Importin 8
IPO9	Importin 9
IPO11	Importin 11
IPO13	Importin 13
KIF26B	Kinesin family member 26B
KING	Efficacy and Safety of Selinexor (KPT-330) in Recurrent Glioblastoma trial
KPN	Karyopherin
KPNA	Karyopherin α
KPNA1	Karyopherin α1; importin-α5
KPNA2	Karyopherin α2; importin-α1
KPNA3	Karyopherin α3; importin-α4
KPNA4	Karyopherin α4; importin-α3
KPNA5	Karyopherin α5; importin-α6
KPNA6	Karyopherin α6; importin-α7
KPNA7	Karyopherin α7; importin-α8
KPNB1	Karyopherin β1; importin-β1
KU70	Ku autoantigen, 70 kDa subunit; encoded by XRCC6
MAGOH	Mago homologue, exon junction complex subunit
MAGOHB	Mago homologue B, exon junction complex subunit
MAPK	Mitogen-activated protein kinase
Mcl-1	Myeloid cell leukaemia 1 protein
MFN2	Mitofusin 2
MGMT	O^6-methylguanine-DNA methyltransferase
MIB1	MIB-1 antibody clone recognising the Ki-67 proliferation antigen
miR/miRNA	MicroRNA
MiT/TFE	Microphthalmia/transcription factor E family
MITF	Melanocyte-inducing transcription factor
MKNK2	MAP kinase-interacting serine/threonine kinase 2
MKNK2b	Splice isoform b of MAP kinase-interacting serine/threonine kinase 2
mRNA	Messenger RNA
MSI2	Musashi RNA-binding protein 2
mTOR	Mechanistic target of rapamycin
MYC/c-MYC	MYC proto-oncogene protein; c-Myc
N-MYC	N-Myc proto-oncogene protein; encoded by MYCN
NAT10	N-acetyltransferase 10
NCT	Nucleocytoplasmic transport
NES	Nuclear export signal
NF-κB	Nuclear factor κB
NLGN3	Neuroligin 3
NLS	Nuclear localisation signal
NOP56/NOP58	NOP56 and NOP58 ribonucleoproteins
NPAT	Nuclear protein, coactivator of histone transcription
NRAS	NRAS proto-oncogene GTPase
NRP1	Neuropilin 1

NSCLC	Non-small-cell lung cancer
NSUN2	NOP2/Sun RNA methyltransferase 2
p21	Cyclin-dependent kinase inhibitor 1A; encoded by CDKN1A
p27	Cyclin-dependent kinase inhibitor 1B; encoded by CDKN1B
p50RhoGAP	Rho GTPase-activating protein 1; encoded by ARHGAP1
p53	Tumour suppressor protein p53; encoded by TP53
P300	Histone acetyltransferase p300; encoded by EP300
PDAC	Pancreatic ductal adenocarcinoma
PDCD5	Programmed cell death 5
PFKP	Phosphofructokinase, platelet isoform
Pfn-1	Profilin-1
PFS6	Progression-free survival at six months
PI3K	Phosphoinositide 3-kinase
PKA	Protein kinase A
PKM2	Pyruvate kinase M2
pRb/RB	Retinoblastoma protein; encoded by RB1
pre-miRNA	Precursor microRNA
PRKDC	Protein kinase, DNA-activated, catalytic subunit; gene encoding DNA-PKcs
PTEN	Phosphatase and tensin homologue
PTPN4	Protein tyrosine phosphatase non-receptor type 4
PY	Proline–tyrosine motif
PY-NLS	Proline–tyrosine nuclear localisation signal
Ran	Ras-related nuclear protein
RanBP3	Ran-binding protein 3
RanGTP	GTP-bound Ran
RAS	Rat sarcoma family of small GTPases
RASAL2	RAS protein activator-like 2
RBM8A/Y14	RNA-binding motif protein 8A; also known as Y14
RCC1	Regulator of chromosome condensation 1
RFPL3	Ret finger protein-like 3
RNA	Ribonucleic acid
RNAi	RNA interference
RNF31	Ring finger protein 31
RNF180	Ring finger protein 180
ROS	Reactive oxygen species
RPRM	Reprimo
RREB1	RAS-responsive element-binding protein 1
RSY-NLS	Arginine–serine–tyrosine-rich nuclear localisation signal
SAC	Spindle assembly checkpoint
SEC	Super elongation complex
shRNA	Short hairpin RNA
SINE	Selective inhibitor of nuclear export
SIRT6	Sirtuin 6
SLC25A10	Solute carrier family 25 member 10
SLX4	SLX4 structure-specific endonuclease subunit
SMAD	SMAD family proteins; name derived from Sma and Mothers against decapentaplegic
SMAD3	SMAD family member 3
SNAI1	Snail family transcriptional repressor 1
SNHG6	Small nucleolar RNA host gene 6
SNP	Single-nucleotide polymorphism
SOX2	SRY-box transcription factor 2
SP1	Specificity protein 1
SR	Serine/arginine-rich
SRSF1	Serine/arginine-rich splicing factor 1

SRY	Sex-determining region Y
STAT3	Signal transducer and activator of transcription 3
STMN1	Stathmin 1
STORM	Selinexor Treatment of Refractory Myeloma trial
STRAD	STE20-related adaptor; STRADα in the cited XPO7 study
SUMO	Small ubiquitin-like modifier; SUMOylation denotes its conjugation to substrates
SWI/SNF	Switch/sucrose non-fermentable chromatin-remodelling complex
TAU	Microtubule-associated protein tau; encoded by MAPT
TCF3	Transcription factor 3
TCGA	The Cancer Genome Atlas
TDP-43	TAR DNA-binding protein 43
TFE3	Transcription factor E3
TNBC	Triple-negative breast cancer
TNF-α	Tumour necrosis factor α
TNPO1	Transportin 1; karyopherin-β2
TNPO2	Transportin 2; importin 3
TNPO3	Transportin 3; transportin-SR2; importin 12
TP53	Tumour protein p53 gene
TPR	Translocated promoter region, nuclear basket protein
TRAF2	TNF receptor-associated factor 2
tRNA	Transfer RNA
TUBB3	Tubulin β3 class III
UBC9	Ubiquitin-conjugating enzyme 9; SUMO-conjugating enzyme encoded by UBE2I
UBE2E1	Ubiquitin-conjugating enzyme E2 E1
UBE2O	Ubiquitin-conjugating enzyme E2 O
USP7	Ubiquitin-specific peptidase 7
USP22	Ubiquitin-specific peptidase 22
UV	Ultraviolet
WHO	World Health Organization
WNT	Wingless-related integration site signalling family
XPA	Xeroderma pigmentosum complementation group A protein
XPO1	Exportin 1; also known as CRM1
XPO2	Exportin 2; also known as CSE1L or CAS
XPO3/XPOT	Exportin-t; transfer RNA export receptor
XPO4	Exportin 4
XPO5	Exportin 5
XPO6	Exportin 6
XPO7	Exportin 7
YAP	Yes-associated protein
YBX1	Y-box-binding protein 1
ZNF143	Zinc finger protein 143

Appendix A

Table A1. Karyopherins, their cargoes and implicated cancers.

ID *	KPN	Cargos	Oncopathology	Expression
Exportins				
12825	XPO1, CRM1	p53, FOXO3a, phosphorylated RB, p21, p27, survivin	Glioblastoma (GBM); multiple myeloma; diffuse large B-cell lymphoma; paediatric solid/CNS tumours; paediatric high-grade glioma; medulloblastoma discussed prospectively	↑ in GBM: associated with cytoplasmic redistribution of tumour suppressors. XPO1 inhibition has antitumour effects, with clinical efficacy demonstrated in multiple myeloma [2,11,12,14]
2431	XPO2, CSE1L, CAS	importin-α family members	Oral cancer; gastric cancer; colon adenocarcinoma; broader pan-cancer associations	↑: associated with invasion, metastasis, advanced stage/grade and poorer outcomes. Depletion suppresses malignant behaviour or increases treatment sensitivity in selected models. Effects on apoptosis are context dependent [28–31].
12826	XPO3, XPOT	tRNAs	Breast cancer; hepatocellular carcinoma (HCC); neuroblastoma	Inhibition suppresses breast cancer progression. Proposed prognostic marker in HCC and therapeutic target in neuroblastoma [36–38]
17675	XPO5, KIAA1291	pre-miRNAs, synthetic shRNAs, dsRNAs; dsRNA-binding-domain-containing cargoes are also mentioned	Melanoma; colorectal, gastric, thyroid, laryngeal, oesophageal and renal cancers; non-small-cell lung cancer (NSCLC); multiple myeloma; triple-negative breast cancer (TNBC); liver cancer	↑: associated with progression in melanoma, colorectal and gastric cancers. ↓/impaired function: linked to cancer susceptibility or progression in some settings. Low-expression-associated variants correlate with better treatment response/survival in NSCLC and myeloma. Depletion suppresses TNBC progression. ERK-mediated inhibition is associated with adverse outcomes in liver cancer [42–44,48].
19733	XPO6, RANBP20, KIAA0370, FLJ22519	actin–profilin-1 complexes	Breast cancer; bladder and pancreatic cancers through the discussion of profilin-1	Depletion in breast cancer: increases nuclear profilin-1 and represses MYC transcription. Bladder/pancreatic findings concern profilin-1 [58].
Importins				
6394	KPNA1, IPOA5, SRP1, RCH2, NPI-1	Import: ESRRA, NSUN2, DDX21, NOP58, NOP56, fibrillarin	Oesophageal squamous cell carcinoma; bladder cancer. Indirect links through nucleolar partners: TNBC, HCC, leukaemia, colorectal and lung cancers	Supports ESRRA-associated macrophage polarisation and NSUN2-dependent bladder cancer progression [71,72].
6395	KPNA2, IPOA1, RCH1, SRP1α, QIP2, PTAC58; RAG cohort 1	Import: c-MYC, N-MYC, p53, Norrin; ALYREF with KPNB1, mentioned in the IPO13 section	GBM; glioma/infiltrative astrocytoma; medulloblastoma, principally as a proposed mechanism; TNBC through the ALYREF transport discussion	↑ in glioma/GBM: associated with higher grade, proliferation and poorer survival; supports MYC-dependent metabolism and Norrin–Notch signalling. Depletion: causes growth arrest/apoptosis in models. Medulloblastoma dependence remains unvalidated [74–76].
6396	KPNA3, IPOA4, SRP1γ, SRP4, hSRP1	Import: RCC1, RanBP3, XPA	Chronic lymphocytic leukaemia; mantle cell lymphoma; skin cancer and HCC through XPA biology	↓ through miR-223: linked in to reduced NF-κB signalling in leukaemia/lymphoma. A consistent tumour-promoting or tumour-suppressive expression relationship is not established. Skin/HCC links are indirect [82,85].

6397	KPNA4, IPOA3, QIP1, SRP3, MGC12217MGC26703	Import/localisation-linked proteins: RCC1, RanBP3, RREB1, p53, hMSH2, NF-κB. miR-181b and miR-567 are regulatory associations, not established cargoes	Prostate and breast cancers; head and neck squamous cell carcinoma; GBM; papillary thyroid cancer; pancreatic ductal adenocarcinoma (PDAC); NSCLC; HCC	↑: associated with aggressive disease, metastasis, poorer survival and treatment resistance. Ser60 phosphorylation increases RREB1 import. Depletion: suppresses malignant phenotypes and can restore treatment sensitivity. Hypoxia-associated elevation contributes to resistance in HCC models [93,97,99].
6398	KPNA5 IPOA6, SRP6	Import: PTPN4	Breast, pancreatic and ovarian cancers	↓ in breast and ovarian cancers. In ovarian cancer, low expression correlates with adverse clinical features; experimental overexpression suppresses tumour growth through PTPN4–STAT3 regulation. ↑ in pancreatic models: improves gemcitabine sensitivity. Functional significance of breast cancer mutations remains unresolved [102–104].
6399	KPNA6 IPOA7, MGC17918 FLJ11249; historical alias KPNA7 †	No specific cancer-relevant cargo established	Chronic myeloid leukaemia (CML); lung adenocarcinoma; pan-cancer/head and neck genomic analyses. Also uterine intravenous leiomyomatosis and related smooth-muscle neoplasms	↑ in CML granulocytes and lung adenocarcinoma. Copy-number amplification reported in lung adenocarcinoma; haploinsufficiency reported in uterine neoplasms. Direct functional consequences remain poorly defined [105–108].
21839	KPNA7, IPOA8	No specific cancer-relevant cargo established	Lung adenocarcinoma; breast cancer; gastric cancer; pan-cancer datasets	↑: associated with adverse survival in selected cancers. Depletion in gastric models: reduces proliferation, invasion and xenograft growth and increases apoptosis. Breast cancer findings concern co-occurring genomic alterations rather than demonstrated expression-dependent function [107,109].
6400	KPNB1, IPO1, IPOB, NTF97, IMB1, Impnb, MGC2155, MGC2156, MGC2157	Import: importin-α-bound cargoes, YBX1, SNAI1/Snail, ALYREF with KPNA2. Mitotic regulatory proteins are also discussed	Cervical cancer; GBM; TNBC through the ALYREF transport discussion	↑/increased stability: supports proliferation and GBM progression through YBX1–NLGN3 signalling. Depletion: induces mitotic arrest and apoptosis in cervical cancer models. Nuclear import dependence is also reported in therapy-resistant GBM cells [110,111,113].
6401	TNPO1, KPNB2, IPO2, TRN, MIP, MIP1	Import: ARID1B, FUBP1, BAP1, hnRNP A1, HuR; FUS is also discussed. TDP-43 is mentioned in the chaperone/localisation context	ARID1A-deficient gynaecological cancers; cervical cancer; oesophageal cancer in serum biomarker studies	↑ in ARID1A-deficient models: supports ARID1B import and tumour growth and is associated with poorer prognosis. FUBP1 import supports immune evasion. Transport of tumour-suppressive BAP1 prevents a uniformly oncogenic interpretation. Serum findings remain candidate biomarker evidence [124,126].
19998	TNPO2, IPO3, KPNB2B, TRN2, FLJ12155	Import: hnRNP A1, HuR. Binding/shuttling regulation: ERα, including cytoplasmic retention	Gastric cancer; cervical cancer/HeLa models; breast cancer/MCF-7 models; bladder cancer; head and neck squamous cell carcinoma	↑ in gastric cancer: associated with poorer survival; overexpression promotes proliferation and suppresses apoptosis. Depletion: reverses these effects. Elevated protein in bladder tissue/urine and elevated transcripts in head and neck cancer are observational findings [130,133].
17103	TNPO3, IPO12, TRN-SR, TRN-SR2,	Import: SRSF1 and other SR-rich	Colon adenocarcinoma; mouse fibrosarcoma in a neoantigen study	Depletion: reduces nuclear SRSF1, oncogenic MKNK2 splicing and colon cancer cell

	MTR10A; previous symbol LGMD1F	proteins, CPSF6, CIRBP. EBF1: interacting protein whose nuclear localisation is not TNPO3-dependent		proliferation. Fibrosarcoma evidence concerns immunogenicity of a mutant peptide [134].
19426	IPO4, Imp4, FLJ23338	Import: H3–H4–ASF1 complex, CEBPD, SOX2	Gastric, cervical, bladder and ovarian cancers	↑ in gastric cancer: depletion reduces proliferation/migration. IPO4 supports CEBPD-dependent DNA repair and cisplatin resistance in cervical/bladder models. Impaired IPO4 stability reduces nuclear SOX2 and malignant behaviour in ovarian models [144,146].
6402	IPO5, KPNB3, RANBP5, IMB3, PSE1, MGC2068	Import: BMP receptor-regulated SMADs, RASAL2	Colorectal, oesophageal and cervical cancers	Supports colorectal growth by removing RASAL2 from its cytoplasmic site of RAS inhibition. Depletion: suppresses colorectal and oesophageal tumour phenotypes. ↑ serum IPO5: reported in cervical/oesophageal cancer as candidate biomarker evidence [148].
9852	IPO7, RANBP7, Imp7	Import: GLI1, phosphorylated ERK, GTF2I, MSI2, AR–USP22 complex, YAP, SLC25A10 isoform 3; overlapping MiT/TFE transport with IPO8	GBM; pancreatic and cervical cancers; androgen receptor-positive breast cancer; nasopharyngeal carcinoma; HCC	↑ expression or stability: supports oncogenic nuclear signalling in several models. Depletion/disrupted cargo binding: reduces proliferation or increases drug sensitivity. Dependence varies with cargo availability, hypoxia and signalling state [151,155,157].
9853	IPO8, RANBP8, IMP8	Import: MiT/TFE factors, particularly TFE3; eIF4E; miR-551b-3p in an AGO1-associated complex	Pancreatic cancer; AML; TNBC	Supports the autophagy–lysosome programme in pancreatic cancer and STAT3-associated signalling in TNBC. ↑ IPO8: observed in AML samples; experimental overexpression promotes eIF4E-dependent transformation-associated phenotypes. Depletion: reduces nuclear eIF4E and invasion [159,161].
19425	IPO9, FLJ10402	Import: actin, H2A–H2B, ARID3A, PFKP, ETS-domain transcription factors	Head and neck cancer; T-cell acute lymphoblastic leukaemia; ovarian cancer; breast cancer/MCF-7 models	Supports stemness-associated transcription, leukaemic infiltration and ovarian tumour growth in distinct models. Depletion: can suppress tumour phenotypes, but also protects MCF-7 cells from alliin–paclitaxel-induced apoptosis. No uniform expression–outcome relationship is established [164–166].
20628	IPO11 RanBP11	Import: PTEN, UBE2E1, β-catenin, BZW1/2, TRAF2, RPRM	Lung adenocarcinoma; prostate neoplasia; APC-mutant colorectal cancer; AML; bladder cancer	Loss: destabilises PTEN and promotes lung/prostate neoplasia. Conversely, depletion suppresses β-catenin-dependent colorectal growth and AML growth/engraftment. IPO11 also supports bladder cancer signalling and RPRM-dependent radiosensitivity. Effects are cargo-dependent [169–171].
Bidirectional transporters				
17796	XPO4 FLJ13046, KIAA1721	Export: eIF5A, SMAD3, PKM2, circPPID and selected	HCC; HER2-positive breast cancer; castration-resistant prostate cancer; multiple myeloma; uveal	↓/loss in HCC: associated with tumour formation and poorer survival. ↑ in HER2-positive breast cancer: supports trastuzumab

		circRNAs. Import: SOX2, SRY	melanoma; colon adenocarcinoma; clear-cell renal cell carcinoma; cervical cancer models	resistance. Knockout: increases enzalutamide sensitivity in prostate models. High expression associates with poorer colon cancer but better renal cancer outcomes. Uveal melanoma evidence is a susceptibility-locus association [178,181,182].
14108	XPO7, RANBP16, EXP7, KIAA0745	Export: 14-3-3, p50RhoGAP, STRAD. Nuclear accumulation-linked proteins: p53, NPAT; direct import is not conclusively established. TCF3 abundance is regulated but TCF3 is not an established cargo here	High-grade serous ovarian cancer; small intestinal adenocarcinoma; oligodendroglioma; prostate cancer; Nras-driven mouse liver cancer; AML	↑: associated with poorer survival in ovarian/small intestinal cancer. Loss: promotes liver tumour formation and is associated with adverse prostate outcomes in one study; another prostate study finds tumour-promoting overexpression. In AML, supports p53-associated suppression when TP53 is functional but NPAT-dependent proliferation when TP53 is defective [10,191,194,195].
16853	IPO13 IMP13, RANBP13, KIAA0724	Import: UBC9, MAGOH–RBM8A/Y14, MAGOHB-associated machinery, RFPL3, c-Jun, ALYREF, PDCD5, nuclear clusterin. Export: eIF1A, KU70, SIRT6	Endometrial carcinoma; NSCLC; melanoma; cancers with chromosome 1p/MAGOH loss; TNBC; PDAC; cervical cancer/HeLa models	↑ in endometrial carcinoma, also observed in normal proliferative endometrium. Supports growth or resistance through selected cargoes in NSCLC, melanoma and TNBC. Depletion: suppresses MAGOH-loss-dependent tumours and sensitises resistant TNBC models. Conversely, IPO13 also supports stress-induced apoptosis; depletion can be protective [200,201,204].

* ID: HGNC identifier (HUGO Gene Nomenclature Committee); KPN: karyopherin. ↑, increased expression, abundance or activity; ↓, decreased expression or loss of function. † Historical alias, distinct from the current KPNA7 (importin-α8) gene.

Table A2. Molecular mechanisms/pathways linking karyopherins to oncopathologies.

ID *	KPN	Molecular Mechanisms/Pathways	Oncopathology
Exportins			
12825	XPO1	Tumour suppression and cell-cycle control: nuclear export of p53, FOXO3a, pRb, p21 and p27 impairs their nuclear functions. AND treatment resistance: XPO1 inhibition can induce cytoprotective autophagy; selinexor also activates PKA–CREB signalling and increases MGMT expression, potentially promoting temozolomide resistance [2,12,17,18].	Glioblastoma
2431	XPO2	MITF regulation: supports proliferation and migration [30].	Oral cancer
12826	XPO3	PI3K–AKT–mTOR signalling: implicated in XPOT-associated tumour progression; the mechanistic connection to tRNA export remains incompletely described [39,40].	Breast cancer
17675	XPO5	Exosome-associated tumour progression: XPO5-dependent exosome assembly supports malignant behaviour; silencing XPO5 suppresses progression [45,54].	Triple-negative breast cancer
17675	XPO5	ERK-dependent regulation: phosphorylation inhibits XPO5 function and is associated with treatment resistance [55].	Liver cancer
19733	XPO6	Profilin-1–ENL–MYC regulation: XPO6 depletion increases nuclear profilin-1, enabling repression of MYC transcription through ENL and the super elongation complex [58].	Breast cancer
Importins			

6394	KPNA1	ESRRA–MFN2 regulation: circular RNA-associated nuclear translocation of ESRRA promotes MFN2 expression in tumour-associated macrophages, supporting a tumour-promoting environment [71].	Oesophageal carcinoma
6394	KPNA1	NSUN2 localisation: nuclear translocation of NSUN2 supports tumour progression [72].	Bladder cancer
6395	KPNA2	MYC-dependent metabolism: c-MYC nuclear import supports glycolytic transcription. AND p53 regulation: altered nuclear localisation is linked to autophagy and mesenchymal-like changes. AND Notch signalling: Norrin nuclear import promotes proliferation in glioblastoma stem cells. AND Hippo/YAP signalling: ZNF143-dependent KPNA2 expression is linked to glioma growth and migration [76,77].	Glioma, including glioblastoma
6395	KPNA2	MYC-family regulation: enhanced nuclear accumulation of c-MYC or N-MYC is proposed to amplify oncogenic transcription; direct validation in medulloblastoma remains outstanding [76,79].	Selected MYC-amplified medulloblastomas
6396	KPNA3	XPA-dependent DNA repair: promotes XPA nuclear accumulation following UV-induced damage. The tumour connection is indirect, through XPA biology [82].	Skin cancer; hepatocellular carcinoma
6396	KPNA3	NF-κB signalling: miR-223-mediated KPNA3 downregulation is linked to altered pathway activity [85].	Chronic lymphocytic leukaemia; mantle cell lymphoma
6397	KPNA4	RREB1–miR-143/145 regulation: Ser60 phosphorylation enhances RREB1 nuclear import, suppressing miR-143/145 and sustaining an oncogenic feedback loop [93].	Head and neck squamous cell carcinoma
6397	KPNA4	FAK signalling: increased KPNA4 is mechanistically linked to pathway activity and tumour progression [97].	Pancreatic ductal adenocarcinoma
6397	KPNA4	Hypoxia and mitochondrial regulation: elevated KPNA4 alters mitochondrial content and function, reduces reactive oxygen species and increases treatment resistance [99].	Hepatocellular carcinoma
6398	KPNA5	SNHG6–miR-944–KPNA5 regulation: increased KPNA5 suppresses proliferation and enhances gemcitabine sensitivity; the relevant transport cargo is not specified [103].	Pancreatic cancer
6398	KPNA5	PTPN4–STAT3 signalling: PTPN4 nuclear import reduces STAT3 Tyr705 phosphorylation and suppresses downstream signalling [104].	Ovarian cancer
6399	KPNA6	Expression and genomic alterations are reported, but specific cancer-related cargoes and molecular pathways remain undefined [107,108].	Chronic myeloid leukaemia; lung adenocarcinoma
21839	KPNA7	Depletion increases apoptosis, alters cell-cycle progression and suppresses malignant phenotypes; the responsible cargoes and pathways remain unidentified [109]	Gastric cancer
6400	KPNB1	Mitotic regulation: supports spindle function and cell division; depletion activates the spindle assembly checkpoint and induces mitotic arrest and apoptosis [110,111].	Cervical cancer
6400	KPNB1	USP7–KPNB1–YBX1–NLGN3 regulation: USP7 stabilises KPNB1, supporting YBX1 nuclear import and NLGN3 expression. AND mesenchymal programmes: SNAI1/Snail nuclear import supports invasion [113].	Glioblastoma
6401	TNPO1	Chromatin regulation: ARID1B nuclear import supports proliferation and tumour growth following ARID1A loss [124].	ARID1A-deficient gynaecological cancers
6401	TNPO1	FUBP1–NRP1 regulation: FUBP1 nuclear import regulates NRP1 expression and supports tumour immune evasion [126].	Cervical cancer

19998	TNPO2	DYNC1I1–SP1/P300 regulation: promoter activation increases TNPO2 expression. Depletion increases p21, G1 arrest and apoptosis; the responsible transport cargo remains unidentified [130].	Gastric cancer
19998	TNPO2	HuR-dependent stress responses: depletion increases cytoplasmic HuR and staurosporine-induced apoptosis. AND ERα localisation: binding to activated ERα competes with importin-α and favours cytoplasmic retention [128,129].	Cervical cancer-derived HeLa cells
19998	TNPO2	ERα–AKT signalling: cytoplasmic retention of activated ERα influences signalling; TNPO2 depletion increases nuclear ERα and reduces oestradiol-induced AKT phosphorylation [132].	Breast cancer-derived MCF-7 cells
17103	TNPO3	SRSF1-dependent alternative splicing: nuclear import of SRSF1 supports production of the pro-oncogenic MKNK2b isoform and promotes proliferation [134].	Colon cancer
17103	TNPO3	Antitumour immunity: a mutant TNPO3-derived neoepitope induces tumour-specific CD8 T-cell responses and tumour protection; this is an antigenic effect rather than a transport mechanism [140].	Mouse fibrosarcoma
19426	IPO4	CEBPD–PRKDC–DNA-PKcs regulation: CEBPD nuclear import supports DNA repair and treatment resistance. In hypoxic bladder cancer, IGF2BP2 additionally stabilises IPO4 mRNA [144].	Cervical cancer; bladder cancer
19426	IPO4	SOX2 localisation: IPO4 supports nuclear SOX2 and malignant behaviour; RNF180-mediated IPO4 ubiquitination impairs this localisation [146].	Ovarian cancer
6402	IPO5	RAS signalling: RASAL2 nuclear import reduces its cytoplasmic RAS-inhibitory activity, enhancing signalling and tumour growth [148].	Colorectal cancer
6402	IPO5	Epithelial-to-mesenchymal transition: depletion reduces associated phenotypes and tumour growth; the responsible cargo remains unidentified [148].	Oesophageal cancer
9852	IPO7	FOXM1–IPO7–GLI1 regulation: FOXM1 increases IPO7 expression and promotes GLI1 nuclear localisation [151].	Glioblastoma
9852	IPO7	MAPK/ERK signalling: cingulin stabilises IPO7 mRNA, enhancing nuclear accumulation of phosphorylated ERK [152].	Pancreatic cancer
9852	IPO7	PI3K–AKT–mTOR signalling: GTF2I nuclear import is associated with pathway activation. AND MYC-associated metabolism: MSI2 nuclear import and stabilisation support glycolytic reprogramming [153].	Cervical cancer
9852	IPO7	Androgen receptor signalling: nuclear transport of the AR–USP22 complex supports proliferation; depletion increases enzalutamide responsiveness [155].	Androgen receptor-positive breast cancer
9852	IPO7	YAP signalling: circRILPL1 facilitates YAP nuclear translocation and transcription of cytoskeletal regulators [157].	Nasopharyngeal carcinoma
9852	IPO7	SLC25A10–CEBPB–BCL2A1 regulation: hypoxia-associated import of SLC25A10 isoform 3 supports anti-apoptotic BCL2A1 expression. Disrupting the transport interaction increases etoposide responsiveness [158].	Hepatocellular carcinoma
9853	IPO8	Autophagy–lysosome regulation: nuclear localisation of MiT/TFE transcription factors, particularly TFE3, supports tumour metabolism; IPO7 contributes to overlapping transport requirements [159].	Pancreatic cancer
9853	IPO8	eIF4E-dependent RNA export: IPO8 imports eIF4E into the nucleus. Elevated IPO8 and altered eIF4E localisation are reported in patient samples; functional effects were examined in experimental cell models [160].	Acute myeloid leukaemia
9853	IPO8	miR-551b-3p–STAT3 signalling: AGO1-associated nuclear entry of miR-551b-3p activates STAT3 transcription and an oncostatin signalling programme [161].	Triple-negative breast cancer
19425	IPO9	Chromatin and stemness regulation: let-7-mediated IPO9 repression limits ARID3A nuclear localisation, affecting an ARID3B-containing chromatin-regulatory complex [164].	Head and neck cancer

19425	IPO9	Cyclin D3/CDK6–PFKP–MYC–CXCR4 regulation: PFKP dimerisation exposes an IPO9-recognised nuclear localisation signal; nuclear PFKP increases CXCR4 expression and leukaemic infiltration [165].	T-cell acute lymphoblastic leukaemia
19425	IPO9	Ferroptosis regulation: suppression of HMOX1-dependent ferroptosis supports tumour growth; the responsible transport mechanism remains unresolved [166].	Ovarian cancer
19425	IPO9	Actin-associated apoptosis: depletion reduces nuclear/perinuclear F-actin and protects against apoptosis induced by alliin plus paclitaxel [167].	Breast cancer-derived MCF-7 cells
20628	IPO11	PTEN stability: transport of PTEN and UBE2E1 protects PTEN from cytoplasmic degradation; IPO11 loss promotes PTEN depletion and neoplasia [169].	Lung adenocarcinoma; prostate neoplasia in mice
20628	IPO11	β-catenin signalling: nuclear accumulation of β-catenin supports oncogenic transcription and proliferation [170].	Selected APC-mutant colorectal cancers
20628	IPO11	BZW1/2-dependent growth: nuclear import supports leukaemic growth and stem-cell engraftment; depletion promotes differentiation [171].	Acute myeloid leukaemia
20628	IPO11	KIF26B–TRAF2 regulation: TRAF2 nuclear translocation contributes to tumour progression [172].	Bladder cancer
Bidirectional transporters			
17796	XPO4	eIF5A/SMAD3 localisation: export limits nuclear accumulation; XPO4 loss promotes tumour formation, with eIF5A2 supporting proliferation in XPO4-deficient cells [174,175,178].	Liver cancer models; hepatocellular carcinoma
17796	XPO4	circ-PPID–NAT10–HER2 regulation: cytoplasmic redistribution of circ-PPID permits NAT10-dependent HER2 mRNA stabilisation and supports trastuzumab resistance [181].	HER2-positive breast cancer
17796	XPO4	Knockout increases enzalutamide sensitivity; the responsible cargo and downstream pathway remain unidentified [182].	Castration-resistant prostate cancer
14108	XPO7	TCF3–p21-dependent senescence: maintenance of TCF3 abundance and senescence is linked to tumour suppression [194].	Oncogenic NRAS-driven mouse tumour model
14108	XPO7	Context-dependent growth regulation: loss is associated with poorer outcomes in one study, whereas another reports that elevated XPO7 promotes proliferation, invasion and epithelial-to-mesenchymal transition. The opposing findings remain unresolved [194,195].	Prostate cancer
14108	XPO7	TP53-wild-type context: maintenance of nuclear p53 abundance supports tumour suppression. AND TP53-mutated context: nuclear retention of NPAT supports histone regulation and proliferation. Direct p53 import is not established by nuclear accumulation alone [10].	Acute myeloid leukaemia
16853	IPO13	RFPL3–hTERT regulation: RFPL3 nuclear import supports hTERT promoter occupancy, expression and tumour growth [201].	Non-small-cell lung cancer
16853	IPO13	c-Jun/AP-1 signalling: monomeric α-tubulin stabilises c-Jun and facilitates IPO13-dependent nuclear import [202].	Melanoma
16853	IPO13	Nonsense-mediated mRNA decay: MAGOH/MAGOHB nuclear localisation supports RNA surveillance; MAGOH loss creates dependence on MAGOHB and IPO13-mediated transport [203].	Cancers with hemizygous MAGOH deletion associated with chromosome 1p loss
16853	IPO13	RNF31–ALYREF-dependent RNA export: linear ubiquitination promotes ALYREF nuclear import during paclitaxel treatment, supporting export of TUBB3, STMN1 and TAU mRNAs and treatment resistance [204].	Triple-negative breast cancer

16853	IPO13	UBC9–SLX4-dependent DNA repair: cCCT2 interferes with UBC9 import, reducing SLX4 SUMOylation, stability and condensate formation, thereby enhancing chemotherapy-induced senescence [205].	Pancreatic ductal adenocarcinoma
16853	IPO13	Clusterin/KU70-dependent stress responses: nuclear clusterin import and KU70 export regulate oxidative-stress responses; depletion reduces nuclear clusterin and protects against apoptosis [207].	Cervical cancer-derived HeLa cells

* ID: HGNC identifier (HUGO Gene Nomenclature Committee); KPN: karyopherin. The table summarises mechanisms and disease contexts described in the review. Proposed, indirect and unresolved relationships are identified within the relevant entries.

Appendix B

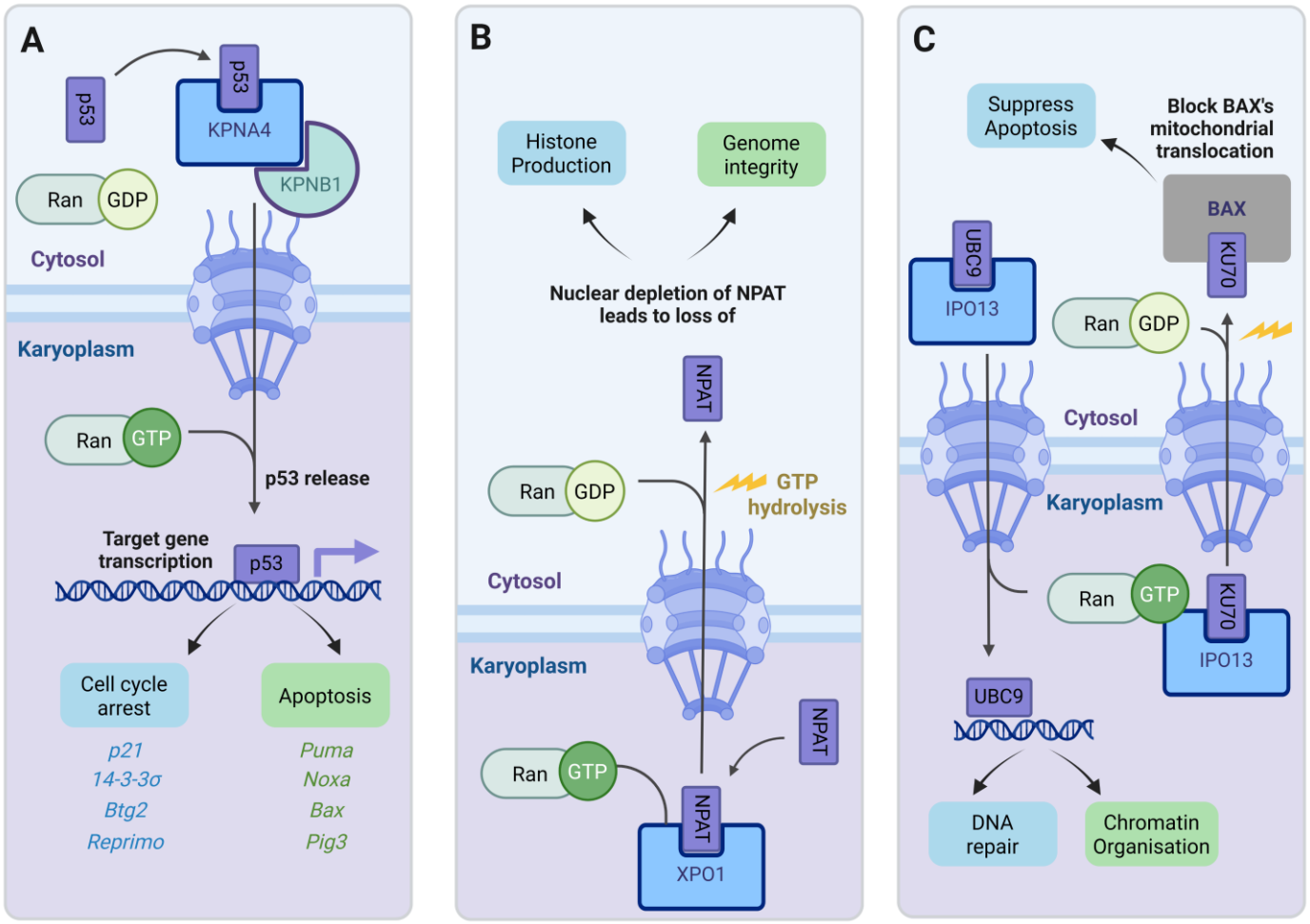


Figure A1. Representative nuclear import, export and bidirectional transport pathways relevant to cancer biology. (A) KPNA4–KPNB1-mediated nuclear import of p53 [5,6,90]. KPNA4 (importin-α3) recognises the nuclear localisation signal of p53 and recruits KPNB1 (importin-β1), which mediates passage through the nuclear pore complex. Nuclear RanGTP promotes import-complex disassembly. Functionally active nuclear p53 regulates transcriptional programmes involved in cell-cycle arrest and apoptosis. (B) XPO1-mediated nuclear export of NPAT [87]. XPO1 (CRM1) recognises a nuclear export signal within the NPAT LisH domain and mediates export to the cytoplasm. Cytoplasmic export-complex disassembly is coupled to RanGTP hydrolysis. XPO1 binding also inhibits NPAT self-association and histone locus body formation. Nuclear NPAT supports histone transcription; its depletion can compromise histone abundance and genome integrity. These downstream consequences of NPAT depletion should be distinguished from the demonstrated mechanism of XPO1-mediated export. (C) Bidirectional transport by IPO13 [196,207]. IPO13 imports UBC9, the

SUMO-conjugating enzyme involved in regulating DNA repair and chromatin-associated proteins, and exports Ku70 under basal conditions. Nuclear Ku70 participates in DNA double-strand-break repair, whereas cytoplasmic Ku70 can bind BAX and inhibit its mitochondrial translocation and pro-apoptotic activity. Ku70 export is sensitive to cellular conditions and decreases during oxidative stress. Each panel is drawn from the cited studies, and the mechanisms shown are those the cited work demonstrated experimentally. Transport pathways are simplified; receptor recycling and accessory factors are omitted. Karyopherins are shown as blue shapes and cargoes as purple boxes; straight arrows indicate the direction of transport through the nuclear pore complex, curved arrows indicate binding, release or downstream effects, and lightning symbols indicate RanGTP hydrolysis. Created in BioRender. Sharipov, D. (2026) https://BioRender.com/fafbytz.

References

1. Hung, M.-C.; Link, W. Protein Localization in Disease and Therapy. *J. Cell Sci.* **2011**, *124*, 3381–3392. https://doi.org/10.1242/jcs.089110.
2. Gravina, G.L.; Senapedis, W.; McCauley, D.; Baloglu, E.; Shacham, S.; Festuccia, C. Nucleo-Cytoplasmic Transport as a Therapeutic Target of Cancer. *J. Hematol. Oncol.* **2014**, *7*, 85. https://doi.org/10.1186/s13045-014-0085-1.
3. Aksu, M.; Pleiner, T.; Karaca, S.; Kappert, C.; Dehne, H.-J.; Seibel, K.; Urlaub, H.; Bohnsack, M.T.; Görlich, D. Xpo7 Is a Broad-Spectrum Exportin and a Nuclear Import Receptor. *J. Cell Biol.* **2018**, *217*, 2329–2340. https://doi.org/10.1083/jcb.201712013.
4. Bayliss, R.; Littlewood, T.; Stewart, M. Structural Basis for the Interaction between FxFG Nucleoporin Repeats and Importin-Beta in Nuclear Trafficking. *Cell* **2000**, *102*, 99–108. https://doi.org/10.1016/s0092-8674(00)00014-3.
5. Cingolani, G.; Petosa, C.; Weis, K.; Müller, C.W. Structure of Importin-Beta Bound to the IBB Domain of Importin-Alpha. *Nature* **1999**, *399*, 221–229. https://doi.org/10.1038/20367.
6. Conti, E.; Uy, M.; Leighton, L.; Blobel, G.; Kuriyan, J. Crystallographic Analysis of the Recognition of a Nuclear Localization Signal by the Nuclear Import Factor Karyopherin Alpha. *Cell* **1998**, *94*, 193–204. https://doi.org/10.1016/s0092-8674(00)81419-1.
7. Pasha, T.; Zatorska, A.; Sharipov, D.; Rogelj, B.; Hortobágyi, T.; Hirth, F. Karyopherin Abnormalities in Neurodegenerative Proteinopathies. *Brain* **2021**, *144*, 2915–2932. https://doi.org/10.1093/brain/awab201.
8. Bischoff, F.R.; Görlich, D. RanBP1 Is Crucial for the Release of RanGTP from Importin Beta-Related Nuclear Transport Factors. *FEBS Lett.* **1997**, *419*, 249–254. https://doi.org/10.1016/s0014-5793(97)01467-1.
9. Izaurralde, E.; Kutay, U.; von Kobbe, C.; Mattaj, I.W.; Görlich, D. The Asymmetric Distribution of the Constituents of the Ran System Is Essential for Transport into and out of the Nucleus. *EMBO J.* **1997**, *16*, 6535–6547. https://doi.org/10.1093/emboj/16.21.6535.
10. Semba, Y.; Yamauchi, T.; Bauer, D.E.; Ogawa, S.; Akashi, K.; Maeda, T. The XPO7-NPAT Axis Represents Key Vulnerabilities in TP53-Mutated Acute Myeloid Leukemia. *Blood* **2026**, *147*, 662–674. https://doi.org/10.1182/blood.2025028918.
11. Grosicki, S.; Simonova, M.; Spicka, I.; Pour, L.; Kriachok, I.; Gavriatopoulou, M.; Pylypenko, H.; Auner, H.W.; Leleu, X.; Doronin, V.; et al. Once-per-Week Selinexor, Bortezomib, and Dexamethasone versus Twice-per-Week Bortezomib and Dexamethasone in Patients with Multiple Myeloma (BOSTON): A Randomised, Open-Label, Phase 3 Trial. *Lancet* **2020**, *396*, 1563–1573. https://doi.org/10.1016/S0140-6736(20)32292-3.
12. Turner, J.G.; Dawson, J.; Sullivan, D.M. Nuclear Export of Proteins and Drug Resistance in Cancer. *Biochem. Pharmacol.* **2012**, *83*, 1021–1032. https://doi.org/10.1016/j.bcp.2011.12.016.
13. Vercruysse, T.; De Bie, J.; Neggers, J.E.; Jacquemyn, M.; Vanstreels, E.; Schmid-Burgk, J.L.; Hornung, V.; Baloglu, E.; Landesman, Y.; Senapedis, W.; et al. The Second-Generation Exportin-1 Inhibitor KPT-8602 Demonstrates Potent Activity against Acute Lymphoblastic Leukemia. *Clin. Cancer Res.* **2017**, *23*, 2528–2541. https://doi.org/10.1158/1078-0432.CCR-16-1580.
14. Lassman, A.B.; Wen, P.Y.; Van Den Bent, M.J.; Plotkin, S.R.; Walenkamp, A.M.E.; Green, A.L.; Li, K.; Walker, C.J.; Chang, H.; Tamir, S.; et al. A Phase II Study of the Efficacy and Safety of Oral Selinexor in Recurrent Glioblastoma. *Clin. Cancer Res.* **2022**, *28*, 452–460. https://doi.org/10.1158/1078-0432.CCR-21-2225.
15. Chari, A.; Vogl, D.T.; Gavriatopoulou, M.; Nooka, A.K.; Yee, A.J.; Huff, C.A.; Moreau, P.; Dingli, D.; Cole, C.; Lonial, S.; et al. Oral Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma. *N. Engl. J. Med.* **2019**, *381*, 727–738. https://doi.org/10.1056/NEJMoa1903455.
16. Food and Drug Administration. *XPOVIO (Selinexor) Tablets, for Oral Use: Highlights of Prescribing Information*; US Food and Drug Administration: Silver Spring, MD, USA, 2026. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/212306s018lbl.pdf (accessed on 20 November 2026).

17. Tang, Y.; Sprinzen, L.; Terada, Y.; Kiang, K.M.; Li, C.; Zeng, Y.; Liu, F.; Zhou, H.; Liang, X.; Zhang, J.; et al. Autophagy Modulates Glioblastoma Cell Sensitivity to Selinexor-Mediated XPO1 Inhibition. *Neuro-Oncol.* **2025**, *27*, 1210–1226. https://doi.org/10.1093/neuonc/noae280.
18. Mapunda, J.A.; Suzuki, Y.; Burgenske, D.; Decker, P.A.; Zhang, L.; Eckel-Passow, J.E.; Sarkaria, J.N.; Kitange, G.J. XPO1-Inhibitor Selinexor Induces MGMT Expression by Activating PKA-CREB Signaling in IDH Wildtype Glioblastoma. *Front. Oncol.* **2025**, *15*, 1633580. https://doi.org/10.3389/fonc.2025.1633580.
19. Otte, K.; Zhao, K.; Braun, M.; Neubauer, A.; Raifer, H.; Helmprobst, F.; Barrera, F.O.; Nimsky, C.; Bartsch, J.W.; Rusch, T. Eltanexor Effectively Reduces Viability of Glioblastoma and Glioblastoma Stem-Like Cells at Nano-Molar Concentrations and Sensitizes to Radiotherapy and Temozolomide. *Biomedicines* **2022**, *10*, 2145. https://doi.org/10.3390/biomedicines10092145.
20. Zhao, K.; Braun, M.; Meyer, L.; Otte, K.; Raifer, H.; Helmprobst, F.; Möschl, V.; Pagenstecher, A.; Urban, H.; Ronellenfitsch, M.W.; et al. A Novel Approach for Glioblastoma Treatment by Combining Apoptosis Inducers (TMZ, MTX, and Cytarabine) with E.V.A. (Eltanexor, Venetoclax, and A1210477) Inhibiting XPO1, Bcl-2, and Mcl-1. *Cells* **2024**, *13*, 632. https://doi.org/10.3390/cells13070632.
21. Van Hauwenhuyse, J.; Reniers, F.; Persoons, L.; Noppen, S.; Wing, C.E.; Niesman, A.B.; Fung, H.Y.J.; Vanstreels, E.; Jacquemyn, M.; Boel, E.; et al. Preclinical Characterization of a Reversible XPO1 Inhibitor for Cancer Therapy. *Nat. Commun.* **2026**, *17*, 8940. https://doi.org/10.1038/s41467-026-75741-y.
22. Princiotto, S.; Jiménez, L.; Domínguez, L.; Sequeira, J.G.N.; Mourato, C.; Orea-Soufi, A.; Santos, B.; Dallavalle, S.; Machuqueiro, M.; Ferreira, B.I.; et al. Chromenone Derivatives as CRM1 Inhibitors for Targeting Glioblastoma. *ChemBioChem* **2025**, *26*, e202500195. https://doi.org/10.1002/cbic.202500195.
23. Green, A.L.; Minard, C.G.; Liu, X.; Safgren, S.L.; Pinkney, K.; Harris, L.; Link, G.; DeSisto, J.; Voss, S.; Nelson, M.D.; et al. Phase I Trial of Selinexor in Pediatric Recurrent/Refractory Solid and CNS Tumors (ADVL1414): A Children's Oncology Group Phase I Consortium Trial. *Clin. Cancer Res.* **2025**, *31*, 1587–1595. https://doi.org/10.1158/1078-0432.CCR-24-2754.
24. Galinski, B.; Alexander, T.B.; Mitchell, D.A.; Chatwin, H.V.; Awah, C.; Green, A.L.; Weiser, D.A. Therapeutic Targeting of Exportin-1 in Childhood Cancer. *Cancers* **2021**, *13*, 6161. https://doi.org/10.3390/cancers13246161.
25. Rallis, K.S.; George, A.M.; Wozniak, A.M.; Bigogno, C.M.; Chow, B.; Hanrahan, J.G.; Sideris, M. Molecular Genetics and Targeted Therapies for Paediatric High-Grade Glioma. *Cancer Genom. Proteom.* **2022**, *19*, 390–414. https://doi.org/10.21873/cgp.20328.
26. Vairy, S.; Michaiel, G. Small-Molecule Drugs in Pediatric Neuro-Oncology. *Curr. Oncol.* **2025**, *32*, 417. https://doi.org/10.3390/curroncol32080417.
27. Scherf, U.; Pastan, I.; Willingham, M.C.; Brinkmann, U. The Human CAS Protein Which Is Homologous to the CSE1 Yeast Chromosome Segregation Gene Product Is Associated with Microtubules and Mitotic Spindle. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 2670–2674. https://doi.org/10.1073/pnas.93.7.2670.
28. Jiang, M.-C. CAS (CSE1L) Signaling Pathway in Tumor Progression and Its Potential as a Biomarker and Target for Targeted Therapy. *Tumour Biol. J. Int. Soc. Oncodev. Biol. Med.* **2016**, *37*, 13077–13090. https://doi.org/10.1007/s13277-016-5301-x.
29. Tai, C.-J.; Hsu, C.-H.; Shen, S.-C.; Lee, W.-R.; Jiang, M.-C. Cellular Apoptosis Susceptibility (CSE1L/CAS) Protein in Cancer Metastasis and Chemotherapeutic Drug-Induced Apoptosis. *J. Exp. Clin. Cancer Res. CR* **2010**, *29*, 110. https://doi.org/10.1186/1756-9966-29-110.
30. Wang, Y.-S.; Peng, C.; Guo, Y.; Li, Y. CSE1L Promotes Proliferation and Migration in Oral Cancer through Positively Regulating MITF. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 5429–5435. https://doi.org/10.26355/eurrev_202005_21327.
31. He, X.; Wang, Y.; Zhang, Y.; Sahu, A.; Almhanna, K.; Liu, Y. CSE1L in Enhancing the Effect of Defactinib on Gastric Cancer Cells via the Inhibition of FAK Phosphorylation. *Transl. Cancer Res.* **2024**, *13*, 6905–6918. https://doi.org/10.21037/tcr-24-2049.
32. Kalia, P.; Nair, R.R.; Yadav, S.S. Analysis of Exportins Expression Unveils Their Prognostic Significance in Colon Adenocarcinoma: Insights from Public Databases. *Discov. Oncol.* **2025**, *16*, 21. https://doi.org/10.1007/s12672-025-01748-4.
33. Li, H.; Wang, L.; Ruan, Z.; Li, X.; Yang, Y.; Fang, J.; Wang, R. CSE1L as a Prognostic Biomarker Associated with Pan Cancer Immune Infiltration and Drug Sensitivity. *Expert Rev. Clin. Immunol.* **2024**, *20*, 1113–1125. https://doi.org/10.1080/1744666X.2024.2356747.
34. Arts, G.J.; Fornerod, M.; Mattaj, I.W. Identification of a Nuclear Export Receptor for tRNA. *Curr. Biol. CB* **1998**, *8*, 305–314. https://doi.org/10.1016/s0960-9822(98)70130-7.
35. Lipowsky, G.; Bischoff, F.R.; Izaurralde, E.; Kutay, U.; Schäfer, S.; Gross, H.J.; Beier, H.; Görlich, D. Coordination of tRNA Nuclear Export with Processing of tRNA. *RNA* **1999**, *5*, 539–549. https://doi.org/10.1017/S1355838299982134.
36. Liang, M.; Wang, M.; Zhu, B. Inhibition of XPOT Promotes Breast Cancer Cell Pyroptosis to Suppress Cancer Progression. *Cent.-Eur. J. Immunol.* **2025**, *50*, 248–259. https://doi.org/10.5114/ceji.2025.154514.

37. Chen, L.; Huang, Y.; Zhou, L.; Lian, Y.; Wang, J.; Chen, D.; Wei, H.; Huang, M.; Huang, Y. Prognostic Roles of the Transcriptional Expression of Exportins in Hepatocellular Carcinoma. *Biosci. Rep.* **2019**, *39*, BSR20190827. https://doi.org/10.1042/BSR20190827.
38. Pan, L.-J.; Chen, J.-L.; Wu, Z.-X.; Wu, Y.-M. Exportin-T: A Novel Prognostic Predictor and Potential Therapeutic Target for Neuroblastoma. *Technol. Cancer Res. Treat.* **2021**, *20*, 15330338211039132. https://doi.org/10.1177/15330338211039132.
39. Hou, Z.; Ma, W.; Ren, D.; Shen, N.; Bi, W.; Guo, M.; Li, X.; Wang, Y.; Jia, H. Exportin-T Promotes Breast Cancer Progression via PI3K/AKT/mTOR Signaling Pathway. *J. Inflamm. Res.* **2025**, *18*, 6467–6481. https://doi.org/10.2147/JIR.S512905.
40. Peng, R.; Li, Y.; Xu, B. Integrating Single-Cell and Bulk RNA Sequencing Data Establishes a Cuproptosis-Related Gene Predictive Signature in Breast Cancer. *Discov. Oncol.* **2025**, *16*, 1775. https://doi.org/10.1007/s12672-025-03525-9.
41. Bohnsack, M.T.; Czaplinski, K.; Görlich, D. Exportin 5 Is a RanGTP-Dependent dsRNA-Binding Protein That Mediates Nuclear Export of Pre-miRNAs. *RNA* **2004**, *10*, 185–191. https://doi.org/10.1261/rna.5167604.
42. Cheng, L.; Wang, P.; Yang, S.; Yang, Y.; Zhang, Q.; Zhang, W.; Xiao, H.; Gao, H.; Zhang, Q. Identification of Genes with a Correlation between Copy Number and Expression in Gastric Cancer. *BMC Med. Genom.* **2012**, *5*, 14. https://doi.org/10.1186/1755-8794-5-14.
43. Ott, C.A.; Linck, L.; Kremmer, E.; Meister, G.; Bosserhoff, A.K. Induction of Exportin-5 Expression during Melanoma Development Supports the Cellular Behavior of Human Malignant Melanoma Cells. *Oncotarget* **2016**, *7*, 62292–62304. https://doi.org/10.18632/oncotarget.11410.
44. Shigeyasu, K.; Okugawa, Y.; Toden, S.; Boland, C.R.; Goel, A. Exportin-5 Functions as an Oncogene and a Potential Therapeutic Target in Colorectal Cancer. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2017**, *23*, 1312–1322. https://doi.org/10.1158/1078-0432.CCR-16-1023.
45. Melo, S.A.; Sugimoto, H.; O'Connell, J.T.; Kato, N.; Villanueva, A.; Vidal, A.; Qiu, L.; Vitkin, E.; Perelman, L.T.; Melo, C.A.; et al. Cancer Exosomes Perform Cell-Independent MicroRNA Biogenesis and Promote Tumorigenesis. *Cancer Cell* **2014**, *26*, 707–721. https://doi.org/10.1016/j.ccell.2014.09.005.
46. Osuch-Wojcikiewicz, E.; Bruzgielewicz, A.; Niemczyk, K.; Sieniawska-Buccella, O.; Nowak, A.; Walczak, A.; Majsterek, I. Association of Polymorphic Variants of miRNA Processing Genes with Larynx Cancer Risk in a Polish Population. *BioMed Res. Int.* **2015**, *2015*, 298378. https://doi.org/10.1155/2015/298378.
47. Wen, J.; Gao, Q.; Wang, N.; Zhang, W.; Cao, K.; Zhang, Q.; Chen, S.; Shi, L. Association of microRNA-Related Gene XPO5 Rs11077 Polymorphism with Susceptibility to Thyroid Cancer. *Medicine* **2017**, *96*, e6351. https://doi.org/10.1097/MD.0000000000006351.
48. Melo, S.A.; Moutinho, C.; Ropero, S.; Calin, G.A.; Rossi, S.; Spizzo, R.; Fernandez, A.F.; Davalos, V.; Villanueva, A.; Montoya, G.; et al. A Genetic Defect in Exportin-5 Traps Precursor microRNAs in the Nucleus of Cancer Cells. *Cancer Cell* **2010**, *18*, 303–315. https://doi.org/10.1016/j.ccr.2010.09.007. Erratum in *Cancer Cell* **2025**, *43*, 1587–1588. https://doi.org/10.1016/j.ccell.2025.07.017.
49. Mishra, P.J.; Mishra, P.J.; Banerjee, D.; Bertino, J.R. MiRSNPs or MiR-Polymorphisms, New Players in microRNA Mediated Regulation of the Cell: Introducing microRNA Pharmacogenomics. *Cell Cycle* **2008**, *7*, 853–858. https://doi.org/10.4161/cc.7.7.5666.
50. de Larrea, C.F.; Navarro, A.; Tejero, R.; Tovar, N.; Díaz, T.; Cibeira, M.T.; Rosiñol, L.; Ferrer, G.; Rovira, M.; Rozman, M.; et al. Impact of MiRSNPs on Survival and Progression in Patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplantation. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2012**, *18*, 3697–3704. https://doi.org/10.1158/1078-0432.CCR-12-0191.
51. Geng, J.-Q.; Wang, X.-C.; Li, L.-F.; Zhao, J.; Wu, S.; Yu, G.-P.; Zhu, K.-J. MicroRNA-Related Single-Nucleotide Polymorphism of XPO5 Is Strongly Correlated with the Prognosis and Chemotherapy Response in Advanced Non-Small-Cell Lung Cancer Patients. *Tumour Biol. J. Int. Soc. Oncodev. Biol. Med.* **2016**, *37*, 2257–2265. https://doi.org/10.1007/s13277-015-3980-3.
52. Horikawa, Y.; Wood, C.G.; Yang, H.; Zhao, H.; Ye, Y.; Gu, J.; Lin, J.; Habuchi, T.; Wu, X. Single Nucleotide Polymorphisms of microRNA Machinery Genes Modify the Risk of Renal Cell Carcinoma. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2008**, *14*, 7956–7962. https://doi.org/10.1158/1078-0432.CCR-08-1199.
53. Ye, Y.; Wang, K.K.; Gu, J.; Yang, H.; Lin, J.; Ajani, J.A.; Wu, X. Genetic Variations in microRNA-Related Genes Are Novel Susceptibility Loci for Esophageal Cancer Risk. *Cancer Prev. Res.* **2008**, *1*, 460–469. https://doi.org/10.1158/1940-6207.CAPR-08-0135.
54. Wang, Z.-W.; Yang, H.-S.; Guo, H.-S.; Li, Y.-Y.; Zhong, J.-Y.; Jiang, S.; Li, J.-P.; Yang, Z.-Y.; Zhou, C.-Y.; Wang, J.; et al. Tumor-Derived Exosomal lncRNA SNHG4 Promotes Triple-Negative Breast Cancer Progression by Targeting XPO5. *Front. Oncol.* **2025**, *15*, 1593827. https://doi.org/10.3389/fonc.2025.1593827.

55. Sun, H.-L.; Cui, R.; Zhou, J.; Teng, K.-Y.; Hsiao, Y.-H.; Nakanishi, K.; Fassan, M.; Luo, Z.; Shi, G.; Tili, E.; et al. ERK Activation Globally Downregulates miRNAs through Phosphorylating Exportin-5. *Cancer Cell* **2016**, *30*, 723–736. https://doi.org/10.1016/j.ccell.2016.10.001.
56. Stüven, T.; Hartmann, E.; Görlich, D. Exportin 6: A Novel Nuclear Export Receptor That Is Specific for Profilin·Actin Complexes. *EMBO J.* **2003**, *22*, 5928–5940. https://doi.org/10.1093/emboj/cdg565.
57. Virtanen, J.A.; Vartiainen, M.K. Diverse Functions for Different Forms of Nuclear Actin. *Curr. Opin. Cell Biol.* **2017**, *46*, 33–38. https://doi.org/10.1016/j.ceb.2016.12.004.
58. Zhu, C.; Kim, S.-J.; Mooradian, A.; Wang, F.; Li, Z.; Holohan, S.; Collins, P.L.; Wang, K.; Guo, Z.; Hoog, J.; et al. Cancer-Associated Exportin-6 Upregulation Inhibits the Transcriptionally Repressive and Anticancer Effects of Nuclear Profilin-1. *Cell Rep.* **2021**, *34*, 108749. https://doi.org/10.1016/j.celrep.2021.108749.
59. Hsu, T.-W.; Huang, T.-L. XPO6 mRNA as a Potential Biomarker for Major Depressive Disorder: Associations with Disease State and Treatment Response. *Neuropsychobiology* **2026**, *85*, 95–103. https://doi.org/10.1159/000550656.
60. Onuma, A.; Fujioka, Y.A.; Fujii, W.; Sugiura, K.; Naito, K. Expression and Function of Exportin 6 in Full-Grown and Growing Porcine Oocytes. *J. Reprod. Dev.* **2019**, *65*, 407–412. https://doi.org/10.1262/jrd.2019-040.
61. Talbot, D.E.; Vormezeele, B.J.; Kimble, G.C.; Wineland, D.M.; Kelpsch, D.J.; Giedt, M.S.; Tootle, T.L. Prostaglandins Limit Nuclear Actin to Control Nucleolar Function during Oogenesis. *Front. Cell Dev. Biol.* **2023**, *11*, 1072456. https://doi.org/10.3389/fcell.2023.1072456.
62. Kutomi, O.; Mizuno, K.; Itoh, T.; Yamada, M. KPNA1/Importin A5 Localizes to the Nucleolus and Associates with Box C/D snoRNP Complexes. *Biochem. Biophys. Res. Commun.* **2026**, *834*, 154505. https://doi.org/10.1016/j.bbrc.2026.154505.
63. Groza, P.; Kumari, K.; Esteva-Socias, M.; Schott, J.; Bhattarai, D.P.; Sajkowska, J.J.; Dasgupta, R.; Peula, C.; Destefanis, E.; Williams, C.; et al. Fibrillarin-Dependent 2′-O-Methylation Modulates RPS28 Ribosome Incorporation and Oncogenic Translation. *Cancer Lett.* **2026**, *639*, 218124. https://doi.org/10.1016/j.canlet.2025.218124.
64. Park, J.E.; Ahn, C.-H.; Sim, D.Y.; Park, S.-Y.; Cha, H.J.; Shim, B.-S.; Kim, B.; Kim, S.-H. NOP56 Drives Colorectal Cancer Progression by Modulating P53 Acetylation through SIRT1/P300. *Int. J. Biol. Sci.* **2026**, *22*, 4537–4554. https://doi.org/10.7150/ijbs.126463.
65. Qian, S.; Liu, H.; Zhang, M.; Zhang, L.; Dai, Y.; Ye, X.; Wen, W.; Cheng, R. Pan-Cancer Landscape Analysis of NOP58 and Its Oncogenic Driving Role in Lung Adenocarcinoma. *Sci. Rep.* **2024**, *14*, 27583. https://doi.org/10.1038/s41598-024-77500-9.
66. Tang, W.; Yang, Y.; Fu, Z.; Xu, W.; Ou, W.; Liu, F.; Du, P.; Liu, C.-Y. The RNA Helicase DDX21 Activates YAP to Promote Tumorigenesis and Is Transcriptionally Upregulated by β-Catenin in Colorectal Cancer. *Oncogene* **2024**, *43*, 3227–3239. https://doi.org/10.1038/s41388-024-03160-8.
67. Wu, H.; Qin, W.; Lu, S.; Wang, X.; Zhang, J.; Sun, T.; Hu, X.; Li, Y.; Chen, Q.; Wang, Y.; et al. Long Noncoding RNA ZFAS1 Promoting Small Nucleolar RNA-Mediated 2′-O-Methylation via NOP58 Recruitment in Colorectal Cancer. *Mol. Cancer* **2020**, *19*, 95. https://doi.org/10.1186/s12943-020-01201-w.
68. Wu, T.; Chalabi-Dchar, M.; Xiong, W.; Arnould, L.; Aimontche, E.; Beaumel, S.; Dumontet, C.; Marcel, V.; Fenouil, T.; Diaz, J.-J.; et al. Fibrillarin Contributes to the Oncogenic Characteristics of Colorectal Cancer Cells and Reduces Sensitivity to 5-Fluorouracil. *Cancers* **2025**, *17*, 3900. https://doi.org/10.3390/cancers17243900.
69. Yang, S.; Liu, J.; Luo, S.; Wang, W.; Xu, J. NOP56 Promotes Hepatocellular Carcinoma Progression through 2′-O-Methylation. *Genes Dis.* **2025**, *12*, 101387. https://doi.org/10.1016/j.gendis.2024.101387.
70. Zhou, F.; Liu, Y.; Rohde, C.; Pauli, C.; Gerloff, D.; Köhn, M.; Misiak, D.; Bäumer, N.; Cui, C.; Göllner, S.; et al. AML1-ETO Requires Enhanced C/D Box snoRNA/RNP Formation to Induce Self-Renewal and Leukaemia. *Nat. Cell Biol.* **2017**, *19*, 844–855. https://doi.org/10.1038/ncb3563.
71. Wang, Y.; Feng, G.; Wang, Y.; Liang, R.; Pan, H.; Lei, K. Tumor-Derived Exosomal circAP2B1 Induces M2 Macrophage Polarization by Enhancing Mitochondrial Homeostasis to Promote Esophageal Squamous Cell Carcinoma Progression. *Adv. Sci.* **2026**, *13*, e76903. https://doi.org/10.1002/advs.76903.
72. Wang, J.-M.; Xie, H.-Y.; Zhang, F.-H.; Shu, X.; Luo, J.-D.; Xie, L.-P.; Li, J.-F. Aberrant KIF26B Expression Promotes Bladder Cancer Progression through Driving NSUN2 Nuclear Localization. *J. Hematol. Oncol.* **2025**, *18*, 110. https://doi.org/10.1186/s13045-025-01749-4.
73. Wang, Z.; Gu, Y.; Liu, Y.; Wang, Z.; Chen, X.; Wang, H.; Zhang, W.; Jin, G.; Cao, X. Phosphorylated Toll-like Receptor 3 Nuclear Translocation in Cancer Cell Promotes Metastasis and Chemoresistance. *Signal Transduct. Target. Ther.* **2025**, *10*, 225. https://doi.org/10.1038/s41392-025-02307-7.
74. Gousias, K.; Becker, A.J.; Simon, M.; Niehusmann, P. Nuclear Karyopherin A2: A Novel Biomarker for Infiltrative Astrocytomas. *J. Neurooncol.* **2012**, *109*, 545–553. https://doi.org/10.1007/s11060-012-0924-2.

75. Chen, Y.; Li, J.; Ma, J.; Bao, Y. ZNF143 Facilitates the Growth and Migration of Glioma Cells by Regulating KPNA2-Mediated Hippo Signalling. *Sci. Rep.* **2023**, *13*, 11097. https://doi.org/10.1038/s41598-023-38158-x.
76. Li, J.; Liu, Q.; Liu, Z.; Xia, Q.; Zhang, Z.; Zhang, R.; Gao, T.; Gu, G.; Wang, Y.; Wang, D.; et al. KPNA2 Promotes Metabolic Reprogramming in Glioblastomas by Regulation of C-Myc. *J. Exp. Clin. Cancer Res.* **2018**, *37*, 194. https://doi.org/10.1186/s13046-018-0861-9.
77. Lu, Y.; Xiao, L.; Liu, Y.; Wang, H.; Li, H.; Zhou, Q.; Pan, J.; Lei, B.; Huang, A.; Qi, S. *MIR517C* Inhibits Autophagy and the Epithelial-to-Mesenchymal (-like) Transition Phenotype in Human Glioblastoma through KPNA2-Dependent Disruption of TP53 Nuclear Translocation. *Autophagy* **2015**, *11*, 2213–2232. https://doi.org/10.1080/15548627.2015.1108507. Correction in *Autophagy* **2019**, *15*, 1125–1127. https://doi.org/10.1080/15548627.2019.1599190.
78. El-Sehemy, A.; Tachibana, N.; Ortin-Martinez, A.; Ringuette, D.; Coyaud, É.; Raught, B.; Dirks, P.; Wallace, V.A. Importin-Alpha Transports Norrin to the Nucleus to Promote Proliferation and Notch Signaling in Glioblastoma Stem Cells. *Oncogene* **2025**, *44*, 1875–1886. https://doi.org/10.1038/s41388-025-03427-8.
79. Northcott, P.A.; Jones, D.T.W.; Kool, M.; Robinson, G.W.; Gilbertson, R.J.; Cho, Y.-J.; Pomeroy, S.L.; Korshunov, A.; Lichter, P.; Taylor, M.D.; et al. Medulloblastomics: The End of the Beginning. *Nat. Rev. Cancer* **2012**, *12*, 818–834. https://doi.org/10.1038/nrc3410.
80. Martinez-Olivera, R.; Datsi, A.; Stallkamp, M.; Köller, M.; Kohtz, I.; Pintea, B.; Gousias, K. Silencing of the Nucleocytoplasmic Shuttling Protein Karyopherin A2 Promotes Cell-Cycle Arrest and Apoptosis in Glioblastoma Multiforme. *Oncotarget* **2018**, *9*, 33471–33481. https://doi.org/10.18632/oncotarget.26033.
81. Pumroy, R.A.; Cingolani, G. Diversification of Importin-α Isoforms in Cellular Trafficking and Disease States. *Biochem. J.* **2015**, *466*, 13–28. https://doi.org/10.1042/BJ20141186.
82. Li, Z.; Musich, P.R.; Cartwright, B.M.; Wang, H.; Zou, Y. UV-Induced Nuclear Import of XPA Is Mediated by Importin-A4 in an ATR-Dependent Manner. *PLoS ONE* **2013**, *8*, e68297. https://doi.org/10.1371/journal.pone.0068297.
83. Deng, Y.; Chen, Q.-S.; Huang, W.-F.; Dai, J.-W.; Wu, Z.-J. XPA Serves as an Autophagy and Apoptosis Inducer by Suppressing Hepatocellular Carcinoma in a PI3K/Akt/mTOR Dependent Manner. *J. Gastrointest. Oncol.* **2021**, *12*, 1797–1810. https://doi.org/10.21037/jgo-21-310.
84. Tanaka, K.; Kamiuchi, S.; Ren, Y.; Yonemasu, R.; Ichikawa, M.; Murai, H.; Yoshino, M.; Takeuchi, S.; Saijo, M.; Nakatsu, Y.; et al. UV-Induced Skin Carcinogenesis in Xeroderma Pigmentosum Group A (XPA) Gene-Knockout Mice with Nucleotide Excision Repair-Deficiency. *Mutat. Res.* **2001**, *477*, 31–40. https://doi.org/10.1016/s0027-5107(01)00093-8.
85. Garding, A.; Bhattacharya, N.; Claus, R.; Ruppel, M.; Tschuch, C.; Filarsky, K.; Idler, I.; Zucknick, M.; Caudron-Herger, M.; Oakes, C.; et al. Epigenetic Upregulation of lncRNAs at 13q14.3 in Leukemia Is Linked to the In Cis Downregulation of a Gene Cluster That Targets NF-kB. *PLoS Genet.* **2013**, *9*, e1003373. https://doi.org/10.1371/journal.pgen.1003373.
86. Xu, S.B.; Gao, X.K.; Liang, H.D.; Cong, X.X.; Chen, X.Q.; Zou, W.K.; Tao, J.L.; Pan, Z.Y.; Zhao, J.; Huang, M.; et al. KPNA3 Regulates Histone Locus Body Formation by Modulating Condensation and Nuclear Import of NPAT. *J. Cell Biol.* **2025**, *224*, e202401036. https://doi.org/10.1083/jcb.202401036.
87. Cong, X.X.; Xu, S.B.; Zou, W.K.; Gao, X.K.; Pan, Z.Y.; Liang, H.D.; Chen, J.; Tao, J.L.; Chen, X.Q.; Chen, R.J.; et al. CRM1 Inhibits NPAT Condensation and Histone Locus Body Formation via a Competitive Occupation Strategy. *J. Cell Biol.* **2026**, *225*, e202412173. https://doi.org/10.1083/jcb.202412173.
88. Bertoli, G.; Cava, C.; Diceglie, C.; Martelli, C.; Rizzo, G.; Piccotti, F.; Ottobrini, L.; Castiglioni, I. MicroRNA-567 Dysregulation Contributes to Carcinogenesis of Breast Cancer, Targeting Tumor Cell Proliferation, and Migration. *Breast Cancer Res. Treat.* **2017**, *161*, 605–616. https://doi.org/10.1007/s10549-016-4079-2.
89. Knudsen, N.Ø.; Nielsen, F.C.; Vinther, L.; Bertelsen, R.; Holten-Andersen, S.; Liberti, S.E.; Hofstra, R.; Kooi, K.; Rasmussen, L.J. Nuclear Localization of Human DNA Mismatch Repair Protein Exonuclease 1 (hEXO1). *Nucleic Acids Res.* **2007**, *35*, 2609–2619. https://doi.org/10.1093/nar/gkl1166.
90. Marchenko, N.; Hanel, W.; Li, D.; Becker, K.; Reich, N.; Moll, U. Stress-Mediated Nuclear Stabilization of P53 Is Regulated by Ubiquitination and Importin-A3 Binding. *Cell Death Differ.* **2010**, *17*, 255–267. https://doi.org/10.1038/cdd.2009.173.
91. Wang, H.; Tao, T.; Yan, W.; Feng, Y.; Wang, Y.; Cai, J.; You, Y.; Jiang, T.; Jiang, C. Upregulation of miR-181s Reverses Mesenchymal Transition by Targeting KPNA4 in Glioblastoma. *Sci. Rep.* **2015**, *5*, 13072. https://doi.org/10.1038/srep13072.
92. Yang, J.; Lu, C.; Wei, J.; Guo, Y.; Liu, W.; Luo, L.; Fisch, G.; Li, X. Inhibition of KPNA4 Attenuates Prostate Cancer Metastasis. *Oncogene* **2017**, *36*, 2868–2878. https://doi.org/10.1038/onc.2016.440.

93. Hazawa, M.; Sakai, K.; Kobayashi, A.; Yoshino, H.; Iga, Y.; Iwashima, Y.; Lim, K.S.; Chih-Cheng Voon, D.; Jiang, Y.-Y.; Horike, S.-I.; et al. Disease-Specific Alteration of Karyopherin-α Subtype Establishes Feed-Forward Oncogenic Signaling in Head and Neck Squamous Cell Carcinoma. *Oncogene* **2020**, *39*, 2212–2223. https://doi.org/10.1038/s41388-019-1137-3.
94. Hazawa, M.; Yoshino, H.; Nakagawa, Y.; Shimizume, R.; Nitta, K.; Sato, Y.; Sato, M.; Wong, R.W.; Kashiwakura, I. Karyopherin-B1 Regulates Radioresistance and Radiation-Increased Programmed Death-Ligand 1 Expression in Human Head and Neck Squamous Cell Carcinoma Cell Lines. *Cancers* **2020**, *12*, 908. https://doi.org/10.3390/cancers12040908.
95. Yan, X.; Mao, X.; Zhu, C.; Lv, G.; Geng, X.; Wu, W.; Ding, Y.; Qin, S.; Wang, X.; Li, Y.; et al. A-to-I Editing Modifies the Target and Role of miR-376a-3p in Papillary Thyroid Cancer. *3 Biotech* **2026**, *16*, 400. https://doi.org/10.1007/s13205-026-04984-9. Erratum in 3 Biotech **2026**, *16*, 503. https://doi.org/10.1007/s13205-026-05119-w.
96. Feng, L.; Wang, R.; Yang, Y.; Shen, X.; Shi, Q.; Lian, M.; Ma, H.; Fang, J. KPNA4 Regulated by miR-548b-3p Promotes the Malignant Phenotypes of Papillary Thyroid Cancer. *Life Sci.* **2021**, *265*, 118743. https://doi.org/10.1016/j.lfs.2020.118743.
97. Bao, J.; Xu, C.; Li, B.; Wu, Z.; Shen, J.; Song, P.; Peng, Q.; Hu, G. Systematic Characterization of the Clinical Relevance of KPNA4 in Pancreatic Ductal Adenocarcinoma. *Front. Oncol.* **2022**, *12*, 834728. https://doi.org/10.3389/fonc.2022.834728. Erratum in *Front. Oncol.* **2023**, *13*, 1282120. https://doi.org/10.3389/fonc.2023.1282120.
98. Hu, S.; Zhang, Q.; Sun, J.; Xue, J.; Wang, C. Circular RNA Circ_0000376 Promotes Paclitaxel Resistance and Tumorigenesis of Non-Small Cell Lung Cancer via Positively Modulating KPNA4 by Sponging miR-1298-5p. *Thorac. Cancer* **2023**, *14*, 2116–2126. https://doi.org/10.1111/1759-7714.14994.
99. Wang, Y.; Li, N.; Qu, L.; Zhang, M.; Li, Z.; Li, X.; Cai, D. Hemoglobin Nanoclusters-Mediated Regulation of KPNA4 in Hypoxic Tumor Microenvironment Enhances Photodynamic Therapy in Hepatocellular Carcinoma. *J. Nanobiotechnol.* **2024**, *22*, 473. https://doi.org/10.1186/s12951-024-02717-9.
100. Jiao, X.; Wood, L.D.; Lindman, M.; Jones, S.; Buckhaults, P.; Polyak, K.; Sukumar, S.; Carter, H.; Kim, D.; Karchin, R.; et al. Somatic Mutations in the Notch, NF-KB, PIK3CA, and Hedgehog Pathways in Human Breast Cancers. *Genes. Chromosomes Cancer* **2012**, *51*, 480–489. https://doi.org/10.1002/gcc.21935.
101. Sjöblom, T.; Jones, S.; Wood, L.D.; Parsons, D.W.; Lin, J.; Barber, T.D.; Mandelker, D.; Leary, R.J.; Ptak, J.; Silliman, N.; et al. The Consensus Coding Sequences of Human Breast and Colorectal Cancers. *Science* **2006**, *314*, 268–274. https://doi.org/10.1126/science.1133427.
102. Mehmood, R.; Jibiki, K.; Shibazaki, N.; Yasuhara, N. Molecular Profiling of Nucleocytoplasmic Transport Factor Genes in Breast Cancer. *Heliyon* **2021**, *7*, e06039. https://doi.org/10.1016/j.heliyon.2021.e06039.
103. Gao, G.; Li, X.; Wu, H.; Huang, L.-L.; Lin, Y.-X.; Huo, Z.; Xiang, Z.-Y.; Zhou, X. LncRNA SNHG6 Upregulates KPNA5 to Overcome Gemcitabine Resistance in Pancreatic Cancer via Sponging miR-944. *Pharmaceuticals* **2023**, *16*, 184. https://doi.org/10.3390/ph16020184.
104. Hu, Y.; Zhou, J.; Ling, X.; Zhao, K.; Huang, P.; Gao, M.; Li, X.; Sun, M.; Zou, Y.; Feng, G. KPNA5 Suppresses Malignant Progression of Ovarian Cancer Through Importing the PTPN4 Into the Nucleus. *Cancer Med.* **2025**, *14*, e70731. https://doi.org/10.1002/cam4.70731.
105. Mascarenhas, C. do C.; Ferreira da Cunha, A.; Brugnerotto, A.F.; Gambero, S.; de Almeida, M.H.; Carazzolle, M.F.; Pagnano, K.B.B.; Traina, F.; Costa, F.F. da; de Souza, C.A. Identification of Target Genes Using Gene Expression Profile of Granulocytes from Patients with Chronic Myeloid Leukemia Treated with Tyrosine Kinase Inhibitors. *Leuk. Lymphoma* **2014**, *55*, 1861–1869. https://doi.org/10.3109/10428194.2013.855311.
106. Buza, N.; Xu, F.; Wu, W.; Carr, R.J.; Li, P.; Hui, P. Recurrent Chromosomal Aberrations in Intravenous Leiomyomatosis of the Uterus: High-Resolution Array Comparative Genomic Hybridization Study. *Hum. Pathol.* **2014**, *45*, 1885–1892. https://doi.org/10.1016/j.humpath.2014.05.010.
107. Lan, X.; Zhao, L.; Zhang, J.; Shao, Y.; Qv, Y.; Huang, J.; Cai, L. Comprehensive Analysis of Karyopherin Alpha Family Expression in Lung Adenocarcinoma: Association with Prognostic Value and Immune Homeostasis. *Front. Genet.* **2022**, *13*, 956314. https://doi.org/10.3389/fgene.2022.956314.
108. Nguyen, P.T.; Shimojukkoku, Y.; Kajiya, Y.; Oku, Y.; Tomishima, A.; Shima, K.; Sasahira, T. Gene Alterations in the Nuclear Transport Receptor Superfamily: A Study of Head and Neck Cancer. *PLoS ONE* **2024**, *19*, e0300446. https://doi.org/10.1371/journal.pone.0300446.
109. Chen, X.; Yue, A.; Wei, H.; Zhang, H.; Sun, W.; Wang, Y. Pan-Cancer Analysis Identifies KPNA7 as a Prognostic and Immune-Related Biomarker with Functional Relevance in Gastric Cancer. *BMC Cancer* **2026**, *26*, 1262. https://doi.org/10.1186/s12885-026-16456-7.

110. Angus, L.; Van Der Watt, P.J.; Leaner, V.D. Inhibition of the Nuclear Transporter, Kpnβ1, Results in Prolonged Mitotic Arrest and Activation of the Intrinsic Apoptotic Pathway in Cervical Cancer Cells. *Carcinogenesis* **2014**, *35*, 1121–1131. https://doi.org/10.1093/carcin/bgt491.
111. Van Der Watt, P.J.; Chi, A.; Stelma, T.; Stowell, C.; Strydom, E.; Carden, S.; Angus, L.; Hadley, K.; Lang, D.; Wei, W.; et al. Targeting the Nuclear Import Receptor Kpnβ1 as an Anticancer Therapeutic. *Mol. Cancer Ther.* **2016**, *15*, 560–573. https://doi.org/10.1158/1535-7163.MCT-15-0052.
112. Kalab, P.; Heald, R. The RanGTP Gradient—A GPS for the Mitotic Spindle. *J. Cell Sci.* **2008**, *121*, 1577–1586. https://doi.org/10.1242/jcs.005959.
113. Li, J.; Zhang, B.; Feng, Z.; An, D.; Zhou, Z.; Wan, C.; Hu, Y.; Sun, Y.; Wang, Y.; Liu, X.; et al. Stabilization of KPNB1 by Deubiquitinase USP7 Promotes Glioblastoma Progression through the YBX1-NLGN3 Axis. *J. Exp. Clin. Cancer Res.* **2024**, *43*, 28. https://doi.org/10.1186/s13046-024-02954-8.
114. Jiang, Y.; Zhao, J.; Liu, Y.; Hu, J.; Gao, L.; Wang, H.; Cui, D. CircKPNB1 Mediates a Positive Feedback Loop and Promotes the Malignant Phenotypes of GSCs via TNF-α/NF-κB Signaling. *Cell Death Dis.* **2022**, *13*, 697. https://doi.org/10.1038/s41419-022-05149-1.
115. Bourmeau, G.; Anezo, O.; Raymond, J.; Ballestín, A.; Pichol-Thievend, C.; Reveilles, J.; Thomas, A.; Wang, L.; Miranda, M.; Moutaux, E.; et al. Proneural–Mesenchymal Hybrid Glioblastoma Cells Are Resistant to Therapy and Dependent on Nuclear Import. *Neuro-Oncol.* **2025**, *27*, 2876–2893. https://doi.org/10.1093/neuonc/noaf160.
116. Mboukou, A.; Rajendra, V.; Kleinova, R.; Tisné, C.; Jantsch, M.F.; Barraud, P. Transportin-1: A Nuclear Import Receptor with Moonlighting Functions. *Front. Mol. Biosci.* **2021**, *8*, 638149. https://doi.org/10.3389/fmolb.2021.638149.
117. Forbes, D.J.; Travesa, A.; Nord, M.S.; Bernis, C. Nuclear Transport Factors: Global Regulation of Mitosis. *Curr. Opin. Cell Biol.* **2015**, *35*, 78–90. https://doi.org/10.1016/j.ceb.2015.04.012.
118. Baade, I.; Hutten, S.; Sternburg, E.L.; Pörschke, M.; Hofweber, M.; Dormann, D.; Kehlenbach, R.H. The RNA-Binding Protein FUS Is Chaperoned and Imported into the Nucleus by a Network of Import Receptors. *J. Biol. Chem.* **2021**, *296*, 100659. https://doi.org/10.1016/j.jbc.2021.100659.
119. Fare, C.M.; Rhine, K.; Lam, A.; Myong, S.; Shorter, J. A Minimal Construct of Nuclear-Import Receptor Karyopherin-B2 Defines the Regions Critical for Chaperone and Disaggregation Activity. *J. Biol. Chem.* **2023**, *299*, 102806. https://doi.org/10.1016/j.jbc.2022.102806.
120. Guo, L.; Kim, H.J.; Wang, H.; Monaghan, J.; Freyermuth, F.; Sung, J.C.; O'Donovan, K.; Fare, C.M.; Diaz, Z.; Singh, N.; et al. Nuclear-Import Receptors Reverse Aberrant Phase Transitions of RNA-Binding Proteins with Prion-like Domains. *Cell* **2018**, *173*, 677–692.e20. https://doi.org/10.1016/j.cell.2018.03.002.
121. Hofweber, M.; Hutten, S.; Bourgeois, B.; Spreitzer, E.; Niedner-Boblenz, A.; Schifferer, M.; Ruepp, M.-D.; Simons, M.; Niessing, D.; Madl, T.; et al. Phase Separation of FUS Is Suppressed by Its Nuclear Import Receptor and Arginine Methylation. *Cell* **2018**, *173*, 706–719.e13. https://doi.org/10.1016/j.cell.2018.03.004.
122. van der Watt, P.J.; Okpara, M.O.; Wishart, A.; Parker, M.I.; Soares, N.C.; Blackburn, J.M.; Leaner, V.D. Nuclear Transport Proteins Are Secreted by Cancer Cells and Identified as Potential Novel Cancer Biomarkers. *Int. J. Cancer* **2022**, *150*, 347–361. https://doi.org/10.1002/ijc.33832.
123. Odnokoz, O.; Banerjee, A.; Cui, X.; Zeng, L.; Uddin, A.; Li, C.; Zhu, Y.; Zhang, M.; Lu, X.; Yarla, N.S.; et al. Disruption of ARID1B Recruitment to the Nuclear Pore Complex as a New Anticancer Therapeutic Strategy. *Adv. Sci.* **2025**, *12*, e15585. https://doi.org/10.1002/advs.202415585.
124. Yang, B.; Chen, J.; Li, X.; Zhang, X.; Hu, L.; Jiang, S.; Zhang, Z.; Teng, Y. TNPO1-Mediated Nuclear Import of ARID1B Promotes Tumor Growth in ARID1A-Deficient Gynecologic Cancer. *Cancer Lett.* **2021**, *515*, 14–27. https://doi.org/10.1016/j.canlet.2021.05.016.
125. Helming, K.C.; Wang, X.; Wilson, B.G.; Vazquez, F.; Haswell, J.R.; Manchester, H.E.; Kim, Y.; Kryukov, G.V.; Ghandi, M.; Aguirre, A.J.; et al. ARID1B Is a Specific Vulnerability in ARID1A-Mutant Cancers. *Nat. Med.* **2014**, *20*, 251–254. https://doi.org/10.1038/nm.3480.
126. Yang, B.; Chen, J.; Teng, Y. TNPO1-Mediated Nuclear Import of FUBP1 Contributes to Tumor Immune Evasion by Increasing NRP1 Expression in Cervical Cancer. *J. Immunol. Res.* **2021**, *2021*, 9994004. https://doi.org/10.1155/2021/9994004.
127. Yang, T.-J.; Li, T.-N.; Huang, R.-S.; Pan, M.Y.-C.; Lin, S.-Y.; Lin, S.; Wu, K.-P.; Wang, L.H.-C.; Hsu, S.-T.D. Tumor Suppressor BAP1 Nuclear Import Is Governed by Transportin-1. *J. Cell Biol.* **2022**, *221*, e202201094. https://doi.org/10.1083/jcb.202201094.
128. Güttinger, S.; Mühlhäusser, P.; Koller-Eichhorn, R.; Brennecke, J.; Kutay, U. Transportin2 Functions as Importin and Mediates Nuclear Import of HuR. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 2918–2923. https://doi.org/10.1073/pnas.0400342101.

129. Rebane, A.; Aab, A.; Steitz, J.A. Transportins 1 and 2 Are Redundant Nuclear Import Factors for hnRNP A1 and HuR. *RNA* **2004**, *10*, 590–599. https://doi.org/10.1261/rna.5224304.
130. Gong, L.; Wen, T.; Li, Z.; Wang, Y.; Wang, J.; Che, X.; Liu, Y.; Qu, X. TNPO2 Operates Downstream of DYNC1I1 and Promotes Gastric Cancer Cell Proliferation and Inhibits Apoptosis. *Cancer Med.* **2019**, *8*, 7299–7312. https://doi.org/10.1002/cam4.2582.
131. von Roretz, C.; Macri, A.M.; Gallouzi, I.-E. Transportin 2 Regulates Apoptosis through the RNA-Binding Protein HuR. *J. Biol. Chem.* **2011**, *286*, 25983–25991. https://doi.org/10.1074/jbc.M110.216184.
132. Moriyama, T.; Yoneda, Y.; Oka, M.; Yamada, M. Transportin-2 Plays a Critical Role in Nucleocytoplasmic Shuttling of Oestrogen Receptor-α. *Sci. Rep.* **2020**, *10*, 18640. https://doi.org/10.1038/s41598-020-75631-3.
133. Chen, Y.-T.; Tu, W.-J.; Ye, Z.-H.; Wu, C.-C.; Ueng, S.-H.; Yu, K.-J.; Chen, C.-L.; Peng, P.-H.; Yu, J.-S.; Chang, Y.-H. Integration of the Cancer Cell Secretome and Transcriptome Reveals Potential Noninvasive Diagnostic Markers for Bladder Cancer. *Proteom. Clin. Appl.* **2024**, *18*, e202300033. https://doi.org/10.1002/prca.202300033.
134. Maertens, G.N.; Cook, N.J.; Wang, W.; Hare, S.; Gupta, S.S.; Öztop, I.; Lee, K.; Pye, V.E.; Cosnefroy, O.; Snijders, A.P.; et al. Structural Basis for Nuclear Import of Splicing Factors by Human Transportin 3. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 2728–2733. https://doi.org/10.1073/pnas.1320755111.
135. Bourgeois, B.; Hutten, S.; Gottschalk, B.; Hofweber, M.; Richter, G.; Sternat, J.; Abou-Ajram, C.; Göbl, C.; Leitinger, G.; Graier, W.F.; et al. Nonclassical Nuclear Localization Signals Mediate Nuclear Import of CIRBP. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 8503–8514. https://doi.org/10.1073/pnas.1918944117.
136. Jang, S.; Cook, N.J.; Pye, V.E.; Bedwell, G.J.; Dudek, A.M.; Singh, P.K.; Cherepanov, P.; Engelman, A.N. Differential Role for Phosphorylation in Alternative Polyadenylation Function versus Nuclear Import of SR-like Protein CPSF6. *Nucleic Acids Res.* **2019**, *47*, 4663–4683. https://doi.org/10.1093/nar/gkz206.
137. Zhou, Q.; Sagmeister, T.; Hutten, S.; Bourgeois, B.; Pavkov-Keller, T.; Dormann, D.; Madl, T. Structural Basis of Phosphorylation-Independent Nuclear Import of CIRBP by TNPO3. *Nat. Commun.* **2025**, *16*, 4456. https://doi.org/10.1038/s41467-025-59802-2.
138. Bayer, M.; Boller, S.; Ramamoothy, S.; Zolotarev, N.; Cauchy, P.; Iwanami, N.; Mittler, G.; Boehm, T.; Grosschedl, R. Tnpo3 Enables EBF1 Function in Conditions of Antagonistic Notch Signaling. *Genes Dev.* **2022**, *36*, 901–915. https://doi.org/10.1101/gad.349696.122.
139. Liu, H.; Gong, Z.; Li, K.; Zhang, Q.; Xu, Z.; Xu, Y. SRPK1/2 and PP1α Exert Opposite Functions by Modulating SRSF1-Guided MKNK2 Alternative Splicing in Colon Adenocarcinoma. *J. Exp. Clin. Cancer Res. CR* **2021**, *40*, 75. https://doi.org/10.1186/s13046-021-01877-y.
140. Duan, F.; Duitama, J.; Al Seesi, S.; Ayres, C.M.; Corcelli, S.A.; Pawashe, A.P.; Blanchard, T.; McMahon, D.; Sidney, J.; Sette, A.; et al. Genomic and Bioinformatic Profiling of Mutational Neoepitopes Reveals New Rules to Predict Anticancer Immunogenicity. *J. Exp. Med.* **2014**, *211*, 2231–2248. https://doi.org/10.1084/jem.20141308.
141. Kimura, M.; Morinaka, Y.; Imai, K.; Kose, S.; Horton, P.; Imamoto, N. Extensive Cargo Identification Reveals Distinct Biological Roles of the 12 Importin Pathways. *eLife* **2017**, *6*, e21184. https://doi.org/10.7554/eLife.21184.
142. Bernardes, N.E.; Fung, H.Y.J.; Li, Y.; Chen, Z.; Chook, Y.M. Structure of IMPORTIN-4 Bound to the H3-H4-ASF1 Histone-Histone Chaperone Complex. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2207177119. https://doi.org/10.1073/pnas.2207177119.
143. Xu, X.; Zhang, X.; Xing, H.; Liu, Z.; Jia, J.; Jin, C.; Zhang, Y. Importin-4 Functions as a Driving Force in Human Primary Gastric Cancer. *J. Cell. Biochem.* **2019**, *120*, 12638–12646. https://doi.org/10.1002/jcb.28530.
144. Zhou, Y.; Liu, F.; Xu, Q.; Yang, B.; Li, X.; Jiang, S.; Hu, L.; Zhang, X.; Zhu, L.; Li, Q.; et al. Inhibiting Importin 4-Mediated Nuclear Import of CEBPD Enhances Chemosensitivity by Repression of PRKDC-Driven DNA Damage Repair in Cervical Cancer. *Oncogene* **2020**, *39*, 5633–5648. https://doi.org/10.1038/s41388-020-1384-3.
145. Yan, Y.; Huang, Z.; Zhu, Z.; Wang, Y.; Cao, X.; Yang, C.; Jiang, J.; Xia, S.; Shen, B. IMP2 Drives Chemoresistance by Repressing Cisplatin-Induced Apoptosis and Ferroptosis via Activation of IPO4 and SLC7A11 under Hypoxia in Bladder Cancer. *Cancer Cell Int.* **2024**, *24*, 386. https://doi.org/10.1186/s12935-024-03570-4.
146. Zhao, H.; Bi, F.; Li, M.; Diao, Y.; Zhang, C. E3 Ubiquitin Ligase RNF180 Impairs IPO4/SOX2 Complex Stability and Inhibits SOX2-Mediated Malignancy in Ovarian Cancer. *Cell. Signal.* **2024**, *113*, 110961. https://doi.org/10.1016/j.cellsig.2023.110961.
147. Baas, R.; Sijm, A.; van Teeffelen, H.A.A.M.; van Es, R.; Vos, H.R.; Marc Timmers, H.T. Quantitative Proteomics of the SMAD (Suppressor of Mothers against Decapentaplegic) Transcription Factor Family Identifies Importin 5 as a Bone Morphogenic Protein Receptor SMAD-Specific Importin. *J. Biol. Chem.* **2016**, *291*, 24121–24132. https://doi.org/10.1074/jbc.M116.748582.
148. Zhang, W.; Lu, Y.; Li, X.; Zhang, J.; Lin, W.; Zhang, W.; Zheng, L.; Li, X. IPO5 Promotes the Proliferation and Tumourigenicity of Colorectal Cancer Cells by Mediating RASAL2 Nuclear Transportation. *J. Exp. Clin. Cancer Res. CR* **2019**, *38*, 296. https://doi.org/10.1186/s13046-019-1290-0.

149. Li, M.; Li, X.; Chen, S.; Zhang, T.; Song, L.; Pei, J.; Sun, G.; Guo, L. IPO5 Mediates EMT and Promotes Esophageal Cancer Development through the RAS-ERK Pathway. *Oxid. Med. Cell. Longev.* **2022**, *2022*, 6570879. https://doi.org/10.1155/2022/6570879.
150. Liu, W.; Patouret, R.; Barluenga, S.; Plank, M.; Loewith, R.; Winssinger, N. Identification of a Covalent Importin-5 Inhibitor, Goyazensolide, from a Collective Synthesis of Furanoheliangolides. *ACS Cent. Sci.* **2021**, *7*, 954–962. https://doi.org/10.1021/acscentsci.1c00056.
151. Xue, J.; Zhou, A.; Tan, C.; Wu, Y.; Lee, H.-T.; Li, W.; Xie, K.; Huang, S. Forkhead Box M1 Is Essential for Nuclear Localization of Glioma-Associated Oncogene Homolog 1 in Glioblastoma Multiforme Cells by Promoting Importin-7 Expression. *J. Biol. Chem.* **2015**, *290*, 18662–18670. https://doi.org/10.1074/jbc.M115.662882.
152. Su, Y.; Wei, F.; Li, S.; Qi, J.; Lin, G.; Li, G.; Liang, P.; Yang, Z.; Long, Y.; Li, X.; et al. Cingulin Is an RNA-Binding Protein Promoting Pancreatic Cancer through Enhancing Importin 7-Mediated Phospho-ERK Nuclear Translocation. *Cell Rep.* **2025**, *44*, 115925. https://doi.org/10.1016/j.celrep.2025.115925.
153. Chen, J.; Hu, Y.; Teng, Y.; Yang, B. Increased Nuclear Transporter Importin 7 Contributes to the Tumor Growth and Correlates With CD8 T Cell Infiltration in Cervical Cancer. *Front. Cell Dev. Biol.* **2021**, *9*, 732786. https://doi.org/10.3389/fcell.2021.732786.
154. Zhou, W.; Qiu, T.; Wang, J.; Chen, J.; Jiang, R.; Teng, Y.; Ma, L.; Bai, Y.; Zhang, R.; Xu, Q. Importin-7 Facilitates Cervical Cancer Progression through MSI2 Nuclear Import and Is Associated with MSI2-MYC-Linked Glycolytic Reprogramming. *Transl. Res. J. Lab. Clin. Med.* **2026**, *293*, 44–62. https://doi.org/10.1016/j.trsl.2026.04.007.
155. Cai, G.-X.; Kong, W.-Y.; Liu, Y.; Zhong, S.-Y.; Liu, Q.; Deng, Y.-F.; Ye, G.-L. Nuclear Transport Maintenance of USP22-AR by Importin-7 Promotes Breast Cancer Progression. *Cell Death Discov.* **2023**, *9*, 211. https://doi.org/10.1038/s41420-023-01525-8.
156. García-García, M.; Sánchez-Perales, S.; Jarabo, P.; Calvo, E.; Huyton, T.; Fu, L.; Ng, S.C.; Sotodosos-Alonso, L.; Vázquez, J.; Casas-Tintó, S.; et al. Mechanical Control of Nuclear Import by Importin-7 Is Regulated by Its Dominant Cargo YAP. *Nat. Commun.* **2022**, *13*, 1174. https://doi.org/10.1038/s41467-022-28693-y.
157. Wu, P.; Hou, X.; Peng, M.; Deng, X.; Yan, Q.; Fan, C.; Mo, Y.; Wang, Y.; Li, Z.; Wang, F.; et al. Circular RNA circRILPL1 Promotes Nasopharyngeal Carcinoma Malignant Progression by Activating the Hippo-YAP Signaling Pathway. *Cell Death Differ.* **2023**, *30*, 1679–1694. https://doi.org/10.1038/s41418-023-01171-8.
158. Liu, D.; Dong, S.; Cheng, S.; Lin, Y.; Chen, S.; Gao, J.; Bi, B.; Li, N.; Mi, J.; Xiong, W. Nuclear Translocation of SLC25A10 Isoform 3 Promotes Chemoresistance in HCC Cells via CEBPB/BCL2A1 Signaling. *Cell Death Dis.* **2026**, *17*, 491. https://doi.org/10.1038/s41419-026-08667-4.
159. Perera, R.M.; Stoykova, S.; Nicolay, B.N.; Ross, K.N.; Fitamant, J.; Boukhali, M.; Lengrand, J.; Deshpande, V.; Selig, M.K.; Ferrone, C.R.; et al. Transcriptional Control of Autophagy-Lysosome Function Drives Pancreatic Cancer Metabolism. *Nature* **2015**, *524*, 361–365. https://doi.org/10.1038/nature14587.
160. Volpon, L.; Culjkovic-Kraljacic, B.; Osborne, M.J.; Ramteke, A.; Sun, Q.; Niesman, A.; Chook, Y.M.; Borden, K.L.B. Importin 8 Mediates m7G Cap-Sensitive Nuclear Import of the Eukaryotic Translation Initiation Factor eIF4E. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 5263–5268. https://doi.org/10.1073/pnas.1524291113.
161. Parashar, D.; Geethadevi, A.; Aure, M.R.; Mishra, J.; George, J.; Chen, C.; Mishra, M.K.; Tahiri, A.; Zhao, W.; Nair, B.; et al. miRNA551b-3p Activates an Oncostatin Signaling Module for the Progression of Triple-Negative Breast Cancer. *Cell Rep.* **2019**, *29*, 4389–4406.e10. https://doi.org/10.1016/j.celrep.2019.11.085.
162. Dopie, J.; Skarp, K.-P.; Rajakylä, E.K.; Tanhuanpää, K.; Vartiainen, M.K. Active Maintenance of Nuclear Actin by Importin 9 Supports Transcription. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, E544–E552. https://doi.org/10.1073/pnas.1118880109.
163. Padavannil, A.; Sarkar, P.; Kim, S.J.; Cagatay, T.; Jiou, J.; Brautigam, C.A.; Tomchick, D.R.; Sali, A.; D'Arcy, S.; Chook, Y.M. Importin-9 Wraps around the H2A-H2B Core to Act as Nuclear Importer and Histone Chaperone. *eLife* **2019**, *8*, e43630. https://doi.org/10.7554/eLife.43630.
164. Liao, T.-T.; Hsu, W.-H.; Ho, C.-H.; Hwang, W.-L.; Lan, H.-Y.; Lo, T.; Chang, C.-C.; Tai, S.-K.; Yang, M.-H. Let-7 Modulates Chromatin Configuration and Target Gene Repression through Regulation of the ARID3B Complex. *Cell Rep.* **2016**, *14*, 520–533. https://doi.org/10.1016/j.celrep.2015.12.064.
165. Gao, X.; Qin, S.; Wu, Y.; Chu, C.; Jiang, B.; Johnson, R.H.; Kuang, D.; Zhang, J.; Wang, X.; Mehta, A.; et al. Nuclear PFKP Promotes CXCR4-Dependent Infiltration by T Cell Acute Lymphoblastic Leukemia. *J. Clin. Invest.* **2021**, *131*, e143119. https://doi.org/10.1172/JCI143119.
166. Meng, Y.; Li, P.; Nair, S. IPO9 Promotes Ovarian Cancer Progression by Suppressing HMOX1-Dependent Ferroptosis. *Hum. Mutat.* **2026**, *2026*, 8545131. https://doi.org/10.1155/humu/8545131.

167. Izdebska, M.; Grzanka, D.; Gagat, M.; Hałas-Wiśniewska, M.; Grzanka, A. Downregulation of Importin-9 Protects MCF-7 Cells against Apoptosis Induced by the Combination of Garlic-Derived Alliin and Paclitaxel. *Oncol. Rep.* **2016**, *35*, 3084–3093. https://doi.org/10.3892/or.2016.4628.
168. McConville, M.; Lankford, K.; Bernardes, N.E.; Walterscheid, A.; Valadez, C.; Niesman, A.; Chook, Y.M.; Liszczak, G. Importin-9 Recognizes the Winged-Helix Fold of ETS Transcription Factors to Mediate Nuclear Import. *Proc. Natl. Acad. Sci. USA* **2026**, *123*, e2536763123. https://doi.org/10.1073/pnas.2536763123.
169. Chen, M.; Nowak, D.G.; Narula, N.; Robinson, B.; Watrud, K.; Ambrico, A.; Herzka, T.M.; Zeeman, M.E.; Minderer, M.; Zheng, W.; et al. The Nuclear Transport Receptor Importin-11 Is a Tumor Suppressor That Maintains PTEN Protein. *J. Cell Biol.* **2017**, *216*, 641–656. https://doi.org/10.1083/jcb.201604025.
170. Mis, M.; O'Brien, S.; Steinhart, Z.; Lin, S.; Hart, T.; Moffat, J.; Angers, S. IPO11 Mediates Bcatenin Nuclear Import in a Subset of Colorectal Cancers. *J. Cell Biol.* **2020**, *219*, e201903017. https://doi.org/10.1083/jcb.201903017.
171. Nachmias, B.; Khan, D.H.; Voisin, V.; Mer, A.S.; Thomas, G.E.; Segev, N.; St-Germain, J.; Hurren, R.; Gronda, M.; Botham, A.; et al. IPO11 Regulates the Nuclear Import of BZW1/2 and Is Necessary for AML Cells and Stem Cells. *Leukemia* **2022**, *36*, 1283–1295. https://doi.org/10.1038/s41375-022-01513-4.
172. Wang, J.-M.; Zhang, F.-H.; Xie, H.-Y.; Liu, Z.-X.; Tang, Y.-J.; Shu, X.; Wu, Y.-Q.; Lu, D.-H.; Sun, J.-Z.; Ying, Y.-F.; et al. KIF26B Promotes Bladder Cancer Progression via Activating Wnt/β-Catenin Signaling in a TRAF2-Dependent Pathway. *Cell Rep.* **2025**, *44*, 115595. https://doi.org/10.1016/j.celrep.2025.115595.
173. Zhang, Y.; Ou, G.; Ye, Z.; Zhou, Z.; Cao, Q.; Li, M.; Wang, J.; Cao, J.; Yang, H. RPRM Negatively Regulates ATM Levels through Its Nuclear Translocation on Irradiation Mediated by CDK4/6 and IPO11. *iScience* **2022**, *25*, 105115. https://doi.org/10.1016/j.isci.2022.105115.
174. Gontan, C.; Güttler, T.; Engelen, E.; Demmers, J.; Fornerod, M.; Grosveld, F.G.; Tibboel, D.; Görlich, D.; Poot, R.A.; Rottier, R.J. Exportin 4 Mediates a Novel Nuclear Import Pathway for Sox Family Transcription Factors. *J. Cell Biol.* **2009**, *185*, 27–34. https://doi.org/10.1083/jcb.200810106.
175. Kurisaki, A.; Kurisaki, K.; Kowanetz, M.; Sugino, H.; Yoneda, Y.; Heldin, C.-H.; Moustakas, A. The Mechanism of Nuclear Export of Smad3 Involves Exportin 4 and Ran. *Mol. Cell. Biol.* **2006**, *26*, 1318–1332. https://doi.org/10.1128/MCB.26.4.1318-1332.2006.
176. Lipowsky, G.; Bischoff, F.R.; Schwarzmaier, P.; Kraft, R.; Kostka, S.; Hartmann, E.; Kutay, U.; Görlich, D. Exportin 4: A Mediator of a Novel Nuclear Export Pathway in Higher Eukaryotes. *EMBO J.* **2000**, *19*, 4362–4371. https://doi.org/10.1093/emboj/19.16.4362.
177. Aksu, M.; Trakhanov, S.; Görlich, D. Structure of the Exportin Xpo4 in Complex with RanGTP and the Hypusine-Containing Translation Factor eIF5A. *Nat. Commun.* **2016**, *7*, 11952. https://doi.org/10.1038/ncomms11952.
178. Zender, L.; Xue, W.; Zuber, J.; Semighini, C.P.; Krasnitz, A.; Ma, B.; Zender, P.; Kubicka, S.; Luk, J.M.; Schirmacher, P.; et al. An Oncogenomics-Based in Vivo RNAi Screen Identifies Tumor Suppressors in Liver Cancer. *Cell* **2008**, *135*, 852–864. https://doi.org/10.1016/j.cell.2008.09.061.
179. Liang, X.-T.; Pan, K.; Chen, M.-S.; Li, J.-J.; Wang, H.; Zhao, J.-J.; Sun, J.-C.; Chen, Y.-B.; Ma, H.-Q.; Wang, Q.-J.; et al. Decreased Expression of XPO4 Is Associated with Poor Prognosis in Hepatocellular Carcinoma. *J. Gastroenterol. Hepatol.* **2011**, *26*, 544–549. https://doi.org/10.1111/j.1440-1746.2010.06434.x.
180. Bhardwaj, A.; Das, S. SIRT6 Deacetylates PKM2 to Suppress Its Nuclear Localization and Oncogenic Functions. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, E538–E547. https://doi.org/10.1073/pnas.1520045113.
181. Wang, S.; Li, Q.; Wang, Y.; Li, X.; Feng, X.; Wei, Y.; Wang, J.; Zhou, X. Peptidylprolyl Isomerase D Circular RNA Sensitizes Breast Cancer to Trastuzumab through Remodeling HER2 N4-Acetylcytidine Modification. *J. Appl. Genet.* **2024**, *65*, 797–807. https://doi.org/10.1007/s13353-024-00840-9.
182. Haldrup, J.; Weiss, S.; Schmidt, L.; Sørensen, K.D. Investigation of Enzalutamide, Docetaxel, and Cabazitaxel Resistance in the Castration Resistant Prostate Cancer Cell Line C4 Using Genome-Wide CRISPR/Cas9 Screening. *Sci. Rep.* **2023**, *13*, 9043. https://doi.org/10.1038/s41598-023-35950-7.
183. de Matos Simoes, R.; Shirasaki, R.; Downey-Kopyscinski, S.L.; Matthews, G.M.; Barwick, B.G.; Gupta, V.A.; Dupéré-Richer, D.; Yamano, S.; Hu, Y.; Sheffer, M.; et al. Genome-Scale Functional Genomics Identify Genes Preferentially Essential for Multiple Myeloma Cells Compared to Other Neoplasias. *Nat. Cancer* **2023**, *4*, 754–773. https://doi.org/10.1038/s43018-023-00550-x.
184. Chen, L.; Wang, Y.; Lin, J.; Song, Z.; Wang, Q.; Zhao, W.; Wang, Y.; Xiu, X.; Deng, Y.; Li, X.; et al. Exportin 4 Depletion Leads to Nuclear Accumulation of a Subset of Circular RNAs. *Nat. Commun.* **2022**, *13*, 5769. https://doi.org/10.1038/s41467-022-33356-z.

185. D'Mellow, M.; Wang, H.; Palmer, J.M.; Hemminki, K.; Cebulla, C.M.; Beasley, A.B.; Bechrakis, N.E.; Pritchard, A.L.; Wadt, K.W.; Johansson, P.A.; et al. GWAS Meta-Analysis Provides New Insights into Uveal Melanoma Risk. *Br. J. Cancer* **2026**, *135*, 983–991. https://doi.org/10.1038/s41416-026-03499-7.
186. Mies, G.; Tsao, N.L.; Houy, A.; Coupland, S.E.; Kalirai, H.; Försti, A.; Hemminki, K.; Thomsen, H.; Stern, M.-H.; Shields, C.L.; et al. Meta-Analysis of Uveal Melanoma Genome-Wide Association Studies Identifies Novel Risk Loci and Population Effect Size Heterogeneity. *HGG Adv.* **2025**, *6*, 100465. https://doi.org/10.1016/j.xhgg.2025.100465.
187. Hao, Y.; Lv, H.; Yan, X.; Liang, Y.; Jiang, A.; Zhao, Y. Multiomics Analysis of Exportin Family Reveals XPO1 as a Novel Target for Clear Cell Renal Cell Carcinoma. *Int. J. Genom.* **2025**, *2025*, 3645641. https://doi.org/10.1155/ijog/3645641.
188. Zhou, M.; Jia, R.; Gao, M.; Yang, J.; Qi, H. TPR Is Required for circRNA, lncRNA and mRNA Nuclear Export. *Non-Coding RNA Res.* **2026**, *17*, 32–43. https://doi.org/10.1016/j.ncrna.2025.11.010.
189. Dorfman, J.; Macara, I.G. STRADα Regulates LKB1 Localization by Blocking Access to Importin-α, and by Association with Crm1 and Exportin-7. *Mol. Biol. Cell* **2008**, *19*, 1614–1626. https://doi.org/10.1091/mbc.e07-05-0454.
190. Mingot, J.; Bohnsack, M.T.; Jäkle, U.; Görlich, D. Exportin 7 Defines a Novel General Nuclear Export Pathway. *EMBO J.* **2004**, *23*, 3227–3236. https://doi.org/10.1038/sj.emboj.7600338.
191. Cáceres-Gorriti, K.Y.; Carmona, E.; Barrès, V.; Rahimi, K.; Létourneau, I.J.; Tonin, P.N.; Provencher, D.; Mes-Masson, A.-M. RAN Nucleo-Cytoplasmic Transport and Mitotic Spindle Assembly Partners XPO7 and TPX2 Are New Prognostic Biomarkers in Serous Epithelial Ovarian Cancer. *PLoS ONE* **2014**, *9*, e91000. https://doi.org/10.1371/journal.pone.0091000.
192. Kim, J.W.; Ylaya, K.; Chung, E.J.; Jun, S.-Y.; Hong, S.-M.; Chung, J.-Y. Prognostic Value of Exportin-7 and Its Association with KRAS Status and Autophagy Markers in Small Intestinal Adenocarcinoma. *Life* **2026**, *16*, 1193. https://doi.org/10.3390/life16071193.
193. Erdem-Eraslan, L.; Heijsman, D.; de Wit, M.; Kremer, A.; Sacchetti, A.; van der Spek, P.J.; Sillevis Smitt, P.A.E.; French, P.J. Tumor-Specific Mutations in Low-Frequency Genes Affect Their Functional Properties. *J. Neurooncol.* **2015**, *122*, 461–470. https://doi.org/10.1007/s11060-015-1741-1.
194. Innes, A.J.; Sun, B.; Wagner, V.; Brookes, S.; McHugh, D.; Pombo, J.; Porreca, R.M.; Dharmalingam, G.; Vernia, S.; Zuber, J.; et al. XPO7 Is a Tumor Suppressor Regulating p21CIP1-Dependent Senescence. *Genes Dev.* **2021**, *35*, 379–391. https://doi.org/10.1101/gad.343269.120.
195. Lin, Y.; Zhan, M.; Xu, B. Exportin XPO7 Acts as an Oncogenic Factor in Prostate Cancer via Upregulation of TCF3. *J. Cancer Res. Clin. Oncol.* **2023**, *149*, 7663–7677. https://doi.org/10.1007/s00432-023-04705-2.
196. Mingot, J.; Kostka, S.; Kraft, R.; Hartmann, E.; Görlich, D. Importin 13: A Novel Mediator of Nuclear Import and Export. *EMBO J.* **2001**, *20*, 3685–3694. https://doi.org/10.1093/emboj/20.14.3685.
197. Baade, I.; Spillner, C.; Schmitt, K.; Valerius, O.; Kehlenbach, R.H. Extensive Identification and In-Depth Validation of Importin 13 Cargoes. *Mol. Cell. Proteom. MCP* **2018**, *17*, 1337–1353. https://doi.org/10.1074/mcp.RA118.000623.
198. Grünwald, M.; Lazzaretti, D.; Bono, F. Structural Basis for the Nuclear Export Activity of Importin13. *EMBO J.* **2013**, *32*, 899–913. https://doi.org/10.1038/emboj.2013.29.
199. Grünwald, M.; Bono, F. Structure of Importin13-Ubc9 Complex: Nuclear Import and Release of a Key Regulator of Sumoylation. *EMBO J.* **2011**, *30*, 427–438. https://doi.org/10.1038/emboj.2010.320.
200. Zeng, B.; Hu, J.; Yuan, R.; Hu, L.; Zhong, L.; Kang, K. Increased Expression of Importin13 in Endometriosis and Endometrial Carcinoma. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* **2012**, *18*, CR361–CR367. https://doi.org/10.12659/msm.882879.
201. Zohud, B.A.; Guo, P.; Zohud, B.A.; Li, F.; Hao, J.J.; Shan, X.; Yu, W.; Guo, W.; Qin, Y.; Cai, X. Importin 13 Promotes NSCLC Progression by Mediating RFPL3 Nuclear Translocation and hTERT Expression Upregulation. *Cell Death Dis.* **2020**, *11*, 879. https://doi.org/10.1038/s41419-020-03101-9.
202. Kappelmann-Fenzl, M.; Kuphal, S.; Krupar, R.; Schadendorf, D.; Umansky, V.; Vardimon, L.; Hellerbrand, C.; Bosserhoff, A.-K. Complex Formation with Monomeric α-Tubulin and Importin 13 Fosters c-Jun Protein Stability and Is Required for c-Jun's Nuclear Translocation and Activity. *Cancers* **2019**, *11*, 1806. https://doi.org/10.3390/cancers11111806.
203. Viswanathan, S.R.; Nogueira, M.F.; Buss, C.G.; Krill-Burger, J.M.; Wawer, M.J.; Malolepsza, E.; Berger, A.C.; Choi, P.S.; Shih, J.; Taylor, A.M.; et al. Genome-Scale Analysis Identifies Paralog Lethality as a Vulnerability of Chromosome 1p Loss in Cancer. *Nat. Genet.* **2018**, *50*, 937–943. https://doi.org/10.1038/s41588-018-0155-3.
204. Huang, S.; Shi, D.; Dai, S.; Jiang, X.; Wang, R.; Yang, M.; Chen, B.; Chen, X.; Kong, L.; He, L.; et al. RNF31 Induces Paclitaxel Resistance by Sustaining ALYREF Cytoplasmic-Nuclear Shuttling in Human Triple-Negative Breast Cancer. *Clin. Transl. Med.* **2025**, *15*, e70203. https://doi.org/10.1002/ctm2.70203.

205. Zhu, S.; Chen, Y.; Lin, H.; Lu, J.; Pan, Y.; Li, G.; Wu, Y.; Zhang, H.; Huang, X.; Chen, Y.; et al. SenExo-cCCT2 Reprograms Senescence Response and Anti-Tumor Immunity Following FOLFIRINOX Chemotherapy in Pancreatic Ductal Adenocarcinoma. *Adv. Sci.* **2025**, *12*, e08431. https://doi.org/10.1002/advs.202508431.
206. Choi, H.-K.; Choi, Y.; Park, E.S.; Park, S.-Y.; Lee, S.-H.; Seo, J.; Jeong, M.-H.; Jeong, J.-W.; Jeong, J.-H.; Lee, P.C.W.; et al. Programmed Cell Death 5 Mediates HDAC3 Decay to Promote Genotoxic Stress Response. *Nat. Commun.* **2015**, *6*, 7390. https://doi.org/10.1038/ncomms8390. Erratum in *Nat. Commun.* **2015**, *6*, 8225, https://doi.org/10.1038/ncomms9225.
207. Gajewska, K.A.; Jans, D.A.; Wagstaff, K.M. The Nuclear Transporter Importin 13 Can Regulate Stress-Induced Cell Death through the Clusterin/KU70 Axis. *Cells* **2023**, *12*, 279. https://doi.org/10.3390/cells12020279.
208. Barling, M.A.L.; Thomas, D.R.; Jans, D.A.; Wagstaff, K.M. The Nuclear Transporter Transportin-3 Functions Under Oxidative Stress. *Cells* **2026**, *15*, 708. https://doi.org/10.3390/cells15080708.
209. Pang, K.; Huang, J.; Zhang, S.; Guan, Y.; Zou, N.; Kang, J.; Du, H.; Zhao, D.; Abramochkin, D.V.; Chen, H.; et al. Translocation of SIRT6 Promotes Glycolysis Reprogramming to Exacerbate Diabetic Angiopathy. *Redox Biol.* **2025**, *85*, 103736. https://doi.org/10.1016/j.redox.2025.103736.

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