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Review

Nucleocytoplasmic Trafficking as an Emerging Determinant of Immune Escape in Multiple Myeloma

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Abstract

Multiple myeloma (MM) remains an incurable plasma cell malignancy despite major advances in immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, bispecific antibodies, and chimeric antigen receptor T-cell therapies. Disease progression and relapse are largely driven by the ability of malignant plasma cells to evade immune surveillance within the bone marrow microenvironment. Although immune escape is traditionally attributed to genomic evolution, immunosuppressive cellular networks, T-cell exhaustion, and impaired antigen presentation, emerging evidence suggests that dysregulated nucleocytoplasmic trafficking may contribute to the regulation of several processes involved in immune escape and may represent a useful conceptual framework for integrating these observations. Exportin-1 (XPO1), the principal nuclear export receptor, regulates the localization and activity of hundreds of proteins involved in tumor suppression, inflammation, antigen processing, interferon signaling, and immune-cell function. XPO1 overexpression, frequently observed in MM, promotes oncogenic signaling while simultaneously reshaping immune responses through altered compartmentalization of transcription factors, cytokine regulators, and stress-response molecules. This review proposes that dysregulated nucleocytoplasmic trafficking may represent an important regulatory framework linking multiple mechanisms of immune escape in MM. We discuss how nuclear export influences tumor immunogenicity, antigen presentation, innate immune sensing, T-cell dysfunction, and remodeling of the bone marrow microenvironment. We further examine how pharmacological inhibition of XPO1 may restore immune surveillance and create therapeutic opportunities for integration with modern immunotherapies. Reframing nuclear export as a potential immune-regulatory process provides a conceptual framework for generating testable hypotheses regarding disease progression, therapeutic resistance, and immune dysfunction in MM.

Keywords: multiple myeloma; immune escape; nucleocytoplasmic trafficking; Exportin-1; selinexor; tumor microenvironment; T-cell; T-cell exhaustion; natural killer cells; antigen presentation; immunotherapy

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Academic Editor: Francesco Pezzella

Received: 1 October 2026
Revised: 24 November 2026
Accepted: 26 November 2026
Published: 27 November 2026

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1. Introduction

The development of multiple myeloma (MM) is driven not only by the intrinsic biology of malignant plasma cells but also by progressive disruption of immune surveillance mechanisms operating within the bone marrow microenvironment. Despite unprecedented therapeutic advances, most patients eventually relapse, highlighting the persistent capacity of myeloma cells to evade host immune control. Increasing evidence indicates that immune escape is not merely a secondary consequence of tumor evolution but rather a central biological process that accompanies clonal selection throughout disease progression [1,2].

Traditional models of immune evasion in MM emphasize defective antigen presentation, expansion of regulatory T cells, accumulation of myeloid-derived suppressor cells, impaired natural killer (NK) cell activity, and establishment of T-cell exhaustion [3]. These mechanisms undoubtedly contribute to disease persistence; however, they are themselves governed by upstream regulatory pathways controlling cellular transcriptional programs and signaling networks.

One such master regulatory system is nucleocytoplasmic trafficking. Nucleocytoplasmic transport is a highly coordinated process that governs the exchange of proteins and RNA between the nucleus and cytoplasm. Proper spatial organization of signaling molecules is essential for cellular homeostasis because numerous transcription factors, tumor suppressors, and immune regulators require controlled nuclear localization to exert their biological functions [4,5].

Dysregulation of this transport machinery profoundly affects cellular fate. Among the proteins involved in nuclear export, exportin-1 (XPO1), also known as chromosome region maintenance protein 1 (CRM1), has emerged as the dominant mediator of nuclear export for more than 200 cargo proteins [6].

In hematologic malignancies, dysregulated XPO1 expression and activity have been associated with aggressive disease features, therapeutic resistance, and adverse clinical outcomes [7]. In MM, increased XPO1 expression may contribute to malignant plasma-cell survival by altering the subcellular localization of tumor suppressors and other regulatory proteins, thereby influencing pathways involved in proliferation, apoptosis, and cellular stress adaptation [8]. However, the biological relevance of XPO1 extends beyond its effects on tumor cells themselves. Nucleocytoplasmic trafficking regulates the availability and activity of transcription factors and signaling molecules involved in inflammatory responses, interferon signaling, antigen presentation, and immune-cell function. Consequently, alterations in nuclear export could influence several processes that collectively determine the effectiveness of antitumor immune surveillance. These include the capacity of malignant cells to present tumor-associated antigens, the activation of innate immune-sensing pathways, the persistence of inflammatory signals within the bone marrow microenvironment, and the functional state of T cells, natural killer cells, and myeloid populations.

Nevertheless, the strength of the evidence supporting these relationships varies across biological contexts. Although the contribution of XPO1 to malignant-cell biology is supported by studies in MM, several proposed links between XPO1-dependent trafficking and immune dysfunction are derived from other tumor models or broader immunological investigations and remain insufficiently characterized in MM. Accordingly, dysregulated nucleocytoplasmic trafficking may provide a useful conceptual framework for examining the interactions between tumor-intrinsic signaling and the immunosuppressive bone marrow microenvironment, rather than representing an already established, independent mechanism of immune escape.

The present review examines nucleocytoplasmic trafficking as a potential regulatory interface linking the intrinsic biology of malignant plasma cells to the immune processes operating within the bone marrow microenvironment. We discuss the biological basis of

XPO1-mediated nuclear export in cancer and its relevance to immune response in MM. We also critically evaluate the available evidence concerning the immunomodulatory effects of pharmacological XPO1 inhibition, including its potential interactions with contemporary immunotherapeutic approaches. By integrating findings from MM with relevant observations from other experimental systems, this review aims to identify convergent mechanisms, distinguish established evidence from plausible but unvalidated hypotheses, and highlight the most important gaps in current knowledge. We propose that dysregulated nucleocytoplasmic trafficking may represent a useful unifying framework for investigating immune escape in MM; however, its specific contribution to individual immune-evasion mechanisms, the cell populations involved, and the clinical relevance of these interactions remain to be established through dedicated mechanistic and translational studies. This perspective may help guide future research toward the identification of biologically meaningful biomarkers and the rational design of combination strategies integrating XPO1-targeted agents with immunotherapy (Figure 1).

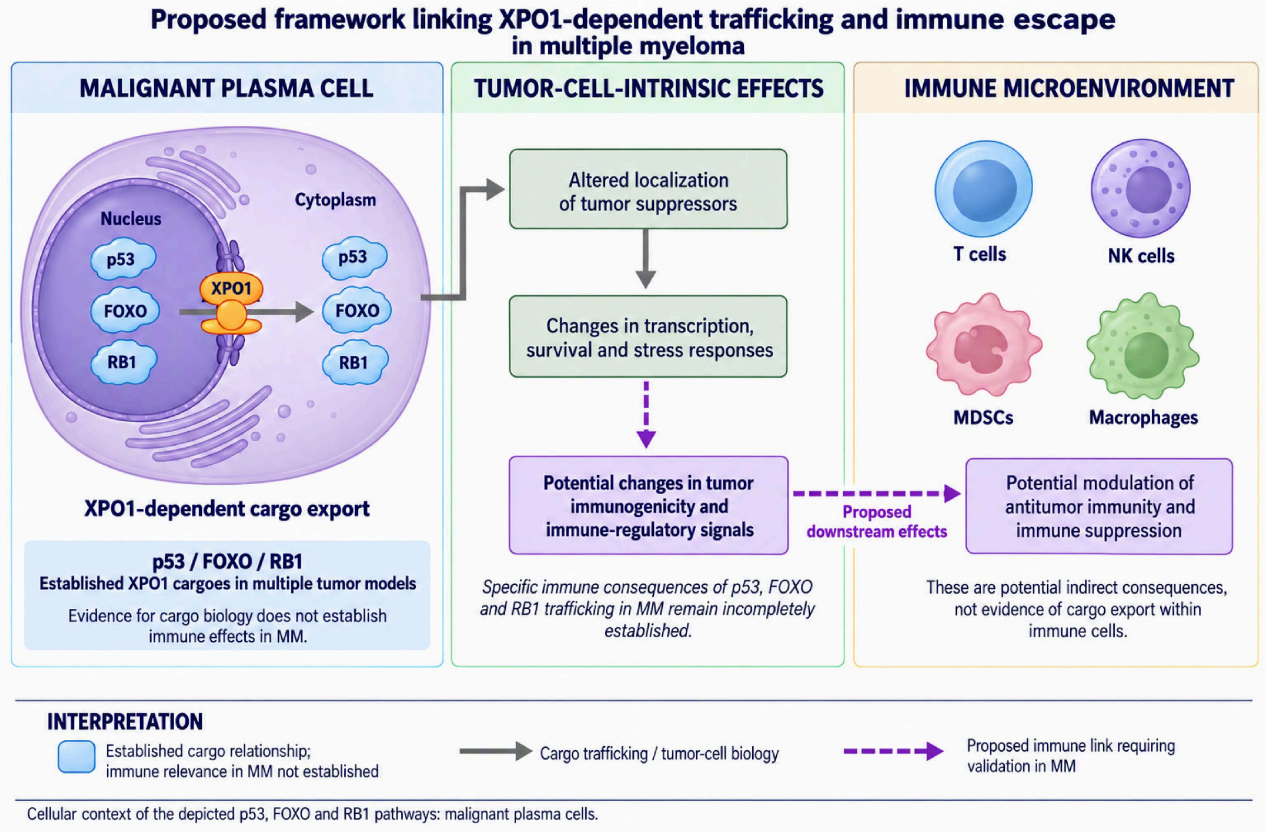

Figure 1. Proposed conceptual model illustrating how XPO1 overexpression may influence interconnected pathways involved in immune surveillance, immune escape, and microenvironmental remodeling in multiple myeloma. The scheme is intended as a hypothesis-generating framework based on currently available experimental evidence. Notably, the strongest experimental evidence concerns XPO1-dependent nuclear export of IκBα and NF-κB/IκBα complexes, whereas alterations in broader NF-κB transcriptional outputs following XPO1 inhibition should be considered downstream consequences rather than evidence of direct export of all pathway components. The pathways involving p53, FOXO, RB1 and NF-κB refer primarily to mechanisms occurring within malignant plasma cells, whereas the effects on T cells, NK cells, MDSCs, macrophages and the bone marrow microenvironment represent downstream or proposed immunological consequences. Abbreviations: XPO1, Exportin-1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.

Literature Search Strategy. This narrative review was based on a structured literature search performed in PubMed, Scopus, and Web of Science up to June 2025. Searches com-

bined terms related to multiple myeloma, nucleocytoplasmic trafficking, XPO1/CRM1 biology, immune escape, antigen presentation, innate immune sensing, NF-κB signaling, T-cell exhaustion, NK-cell dysfunction, and immunotherapy. Priority was given to peer-reviewed original studies, landmark mechanistic reports, translational investigations, and clinically relevant publications. Additional articles were identified through citation tracking of key references. Given the narrative scope of this review, study selection was guided by relevance to the proposed conceptual framework rather than by predefined systematic-review criteria.

2. Biological Basis of Nucleocytoplasmic Trafficking in Cancer

The spatial segregation of nuclear and cytoplasmic functions is a defining feature of eukaryotic cells and represents a fundamental mechanism for controlling cell fate decisions. The nuclear envelope, composed of a double lipid membrane punctuated by nuclear pore complexes (NPCs), establishes a selective barrier that regulates the bidirectional movement of proteins, RNAs, and ribonucleoprotein complexes. Rather than operating as passive channels, NPCs function as dynamic regulatory structures capable of integrating proliferative, stress-related, and environmental signals [9]. Consequently, the intracellular localization of a protein often determines its biological activity as much as its level of expression. Alterations in nucleocytoplasmic transport therefore generate profound consequences for cellular homeostasis by modifying the accessibility of transcription factors, DNA repair proteins, and signaling mediators to their functional compartments.

Bidirectional transport across the nuclear envelope is coordinated by the karyopherin superfamily, which includes importins and exportins. These transport receptors recognize specific amino acid motifs known respectively as nuclear localization signals (NLSs) and nuclear export signals (NESs). Directionality is established by the Ran GTPase cycle, which creates a concentration gradient of Ran-GTP in the nucleus and Ran-GDP in the cytoplasm. The asymmetrical distribution of Ran allows selective assembly and disassembly of transport complexes, ensuring the controlled movement of cargo molecules through NPCs [10,11]. This highly conserved system enables cells to rapidly respond to environmental changes without requiring de novo protein synthesis, providing a powerful mechanism for regulating transcriptional responses to stress, growth factors, cytokines, and genotoxic insults.

Among all exportins, XPO1 is the predominant mediator of nuclear protein export in mammalian cells. XPO1 recognizes leucine-rich NES-containing proteins and facilitates their translocation from the nucleus to the cytoplasm. Proteomic analyses have identified hundreds of XPO1 cargoes, underscoring its role as a master regulator of intracellular organization. These cargoes include proteins involved in cell-cycle control, chromatin remodeling, DNA damage recognition, apoptosis, RNA maturation, and signal transduction. Because such pathways are interconnected, even modest perturbations of XPO1 activity can induce widespread biological consequences that extend across multiple cellular networks simultaneously [4].

An important concept emerging from cancer biology is that nucleocytoplasmic trafficking is not merely a housekeeping function but a critical determinant of oncogenic signaling architecture. Malignant transformation frequently involves reprogramming of protein localization rather than changes in protein abundance alone. Tumor cells can exploit export pathways to alter the intracellular distribution of growth-regulatory molecules, thereby uncoupling signaling networks from their normal physiological constraints. This phenomenon provides a rapid and reversible mechanism for adapting to selective pressures imposed by hypoxia, metabolic stress, immune surveillance, and anticancer therapies. As a result, deregulated nuclear transport is increasingly recognized as a hallmark of aggressive tumor behavior across both solid and hematologic malignancies [12,13].

A central consequence of enhanced XPO1 activity is the functional inactivation of multiple tumor suppressor pathways. While the expression of proteins such as p53, p21, p27, FOXO transcription factors, RB1, and BRCA1 may remain preserved, their excessive export from the nucleus limits access to genomic targets involved in growth arrest, apoptosis, and DNA repair. This mechanism allows malignant cells to attenuate antitumor responses without necessarily acquiring direct genetic alterations in the affected pathways. In this regard, aberrant nuclear export can be viewed as an epigenetic-like regulatory mechanism that reshapes signaling outputs through spatial redistribution of key proteins. Such functional rewiring contributes to cellular plasticity and may facilitate the development of resistance to conventional treatments [14]. Importantly, most evidence supporting XPO1-dependent regulation of p53, FOXO, and RB1 derives from studies performed in diverse tumor models, whereas their specific contribution to immune escape in multiple myeloma remains incompletely characterized.

Beyond its effects on canonical tumor suppressors, altered nucleocytoplasmic trafficking profoundly influences how cancer cells respond to genomic instability. DNA damage responses depend on the coordinated localization of checkpoint proteins, repair complexes, and transcription factors that orchestrate cell-cycle arrest and genome maintenance. Defects in trafficking may disturb these responses, promoting tolerance to DNA lesions and allowing the persistence of genetically heterogeneous clones. The resulting increase in clonal diversity represents an evolutionary advantage for malignant populations, enabling adaptation to changing microenvironmental conditions and therapeutic pressures. Thus, abnormal nuclear export contributes not only to tumor initiation but also to continued disease evolution [15].

Recent studies have also highlighted the intimate relationship between nucleocytoplasmic transport and RNA biology. Numerous RNA-binding proteins and regulatory RNA species undergo continuous trafficking between nuclear and cytoplasmic compartments. Through these interactions, XPO1 influences mRNA stabilization, translation efficiency, and post-transcriptional gene regulation. Dysregulation of these processes can reshape cellular proteomes independently of transcriptional changes, providing an additional layer through which malignant cells optimize survival programs. Importantly, these effects may amplify oncogenic signaling networks by coordinating the expression of functionally related proteins within specific biological pathways [16] (Figure 2).

Collectively, these observations indicate that nucleocytoplasmic trafficking occupies a strategic position at the intersection of genome maintenance, signal transduction, and cellular adaptation. Its deregulation creates a permissive environment for malignant progression by simultaneously influencing multiple biological processes that support cancer-cell survival. This broad regulatory capacity explains why increasing attention has been directed toward nuclear export pathways as therapeutic targets and provides the mechanistic foundation for understanding their relevance in hematologic malignancies such as multiple myeloma.

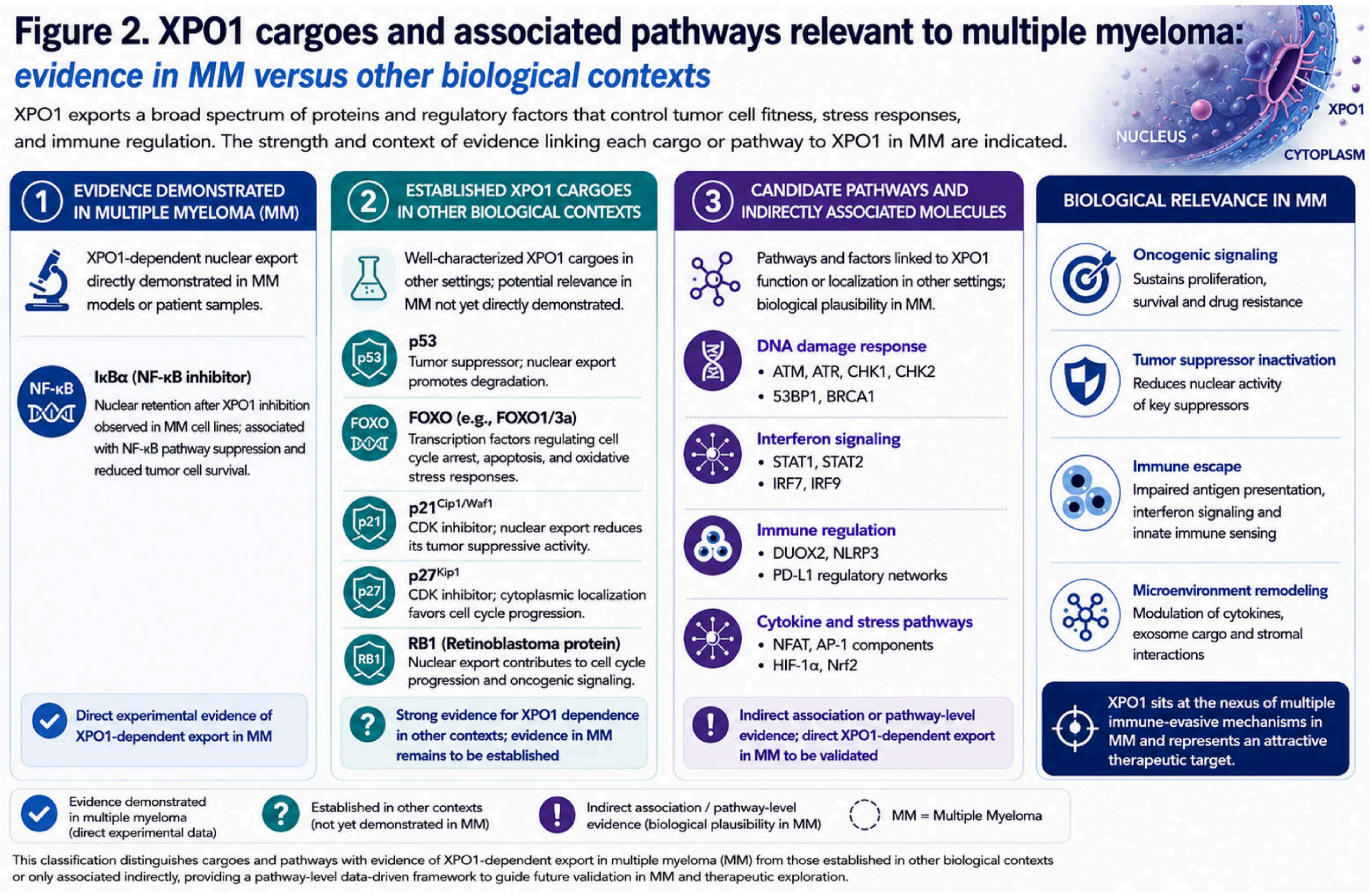

Figure 2. XPO1 cargoes and associated pathways in multiple myeloma (MM). Selected XPO1 cargoes and candidate pathways are classified according to the available evidence: (1) findings experimentally demonstrated in MM models, including IκBα nuclear retention following XPO1 inhibition; (2) established XPO1 cargoes characterized in other biological contexts, whose specific relevance in MM remains to be validated; and (3) candidate pathways supported by indirect or context-dependent evidence. The right panel summarizes their potential implications for tumor progression, immune escape, and bone marrow microenvironment remodeling. Candidate pathways shown in Section 3 represent indirect or context-dependent associations and are not established XPO1 cargoes unless specifically indicated. Abbreviations: MM, multiple myeloma; XPO1, exportin 1; NF-κB, nuclear factor kappa B; FOXO, forkhead box O; RB1, retinoblastoma protein; STAT, signal transducer and activator of transcription; IRF, interferon regulatory factor; NLRP3, NOD-like receptor family pyrin domain containing 3; NFAT, nuclear factor of activated T cells; HIF-1α, hypoxia-inducible factor 1 alpha; NRF2, nuclear factor erythroid 2-related factor 2; PD-L1, programmed death-ligand 1.

3. XPO1 Dysregulation in Multiple Myeloma

Multiple myeloma is highly dependent on coordinated intracellular protein homeostasis, making malignant plasma cells particularly sensitive to perturbations in trafficking pathways. Unlike many other tumor types, myeloma cells continuously synthesize and process large amounts of immunoglobulins, requiring precise integration of transcriptional activity, protein folding, endoplasmic reticulum function, and stress-adaptation mechanisms [17,18].

In this context, XPO1 emerges as a critical hub that supports the dynamic redistribution of regulatory proteins necessary for maintaining malignant fitness. Accordingly, transcriptomic and immunohistochemical studies have consistently demonstrated elevated XPO1 expression in MM compared with normal plasma cells, suggesting that enhanced nuclear export is selected during myeloma pathogenesis rather than representing a secondary epiphenomenon [19].

The biological relevance of XPO1 overexpression in MM extends beyond its effects on individual signaling molecules. Myeloma cells depend on complex transcriptional networks involving MYC, IRF4, BLIMP1, and other lineage-defining factors that control plasma-cell identity and survival [20,21]. Importantly, c-MYC should not be considered an established direct XPO1 cargo in MM. Current evidence suggests that MYC activity may be influenced indirectly by transcriptional and signaling changes induced by XPO1 inhibition, rather than by direct XPO1-mediated nuclear export of MYC itself.

Experimental studies have shown that pharmacological inhibition of XPO1 disrupts these networks and induces profound transcriptional reprogramming, highlighting the central position of nuclear export in maintaining the malignant phenotype [22].

An additional feature that distinguishes MM from many solid tumors is its intimate relationship with proteotoxic stress. Plasma cells operate close to the limits of protein-processing capacity, and malignant transformation further amplifies this burden. To survive under these conditions, myeloma cells activate a variety of adaptive stress-response pathways, including oxidative stress programs and stress-responsive transcriptional regulators [23,24].

XPO1 contributes to the coordination of these adaptive mechanisms by controlling the localization of proteins involved in stress sensing and cellular recovery. Enhanced nuclear export therefore supports the ability of myeloma cells to remain viable despite constant exposure to metabolic and proteostatic challenges. Experimental observations indicating synergy between XPO1 inhibition and proteasome inhibition further underscore the importance of nuclear export in stress adaptation [25].

The role of XPO1 becomes even more evident during disease progression. Relapsed and refractory MM is characterized by increasing biological complexity, with subclonal diversification and acquisition of resistance-associated phenotypes. Analyses of advanced-stage disease suggest that malignant plasma cells progressively develop greater dependence on mechanisms that preserve cellular plasticity in the face of therapeutic pressure [2,26].

By facilitating rapid redistribution of regulatory proteins, aberrant nuclear export allows malignant cells to adapt to changing environmental conditions without requiring permanent genomic alterations. This capacity for dynamic adaptation may be particularly advantageous in heavily pretreated disease, where fluctuating selective pressures continuously reshape tumor architecture [27].

Another important aspect of XPO1 dysregulation in MM concerns its association with high-risk biological features. Increased XPO1 expression has been linked to aggressive disease behavior and inferior clinical outcomes in several hematologic malignancies [28]. The adverse prognostic significance of XPO1 likely reflects its capacity to simultaneously influence multiple pathways involved in survival, DNA-damage tolerance, cellular proliferation, and drug responsiveness.

Rather than acting through a single dominant mechanism, XPO1 appears to function as a central coordinator of diverse processes that collectively enhance malignant fitness. This pleiotropic role may explain why myeloma cells remain highly dependent on nuclear export activity even after developing resistance to multiple therapeutic classes. Importantly, the biological consequences of XPO1 overexpression cannot be fully explained by direct effects on malignant plasma cells alone. MM develops within a specialized bone marrow ecosystem where continuous bidirectional signaling between tumor cells and surrounding stromal elements governs disease behavior [29].

XPO1-regulated pathways influence the production of cytokines, chemokines, and soluble mediators that shape this microenvironmental dialogue. As a result, enhanced nuclear export contributes to remodeling of the tumor niche in ways that support long-term plasma-cell survival. This broader perspective positions XPO1 as a systemic regulator of myeloma biology and provides the conceptual basis for examining how dysregulated

nucleocytoplasmic trafficking may ultimately contribute to immune escape mechanisms throughout disease evolution [6,30].

4. Nucleocytoplasmic Trafficking and Antigen Presentation

Defective antigen presentation represents a central mechanism through which MM cells evade immune surveillance and progressively acquire resistance to immune-mediated elimination. The activation of cytotoxic CD8+ T lymphocytes depends on the efficient generation, processing, and presentation of antigenic peptides by major histocompatibility complex class I (MHC-I) molecules. Loss or attenuation of this machinery has been documented during MM evolution and contributes to impaired immune recognition within the bone marrow microenvironment [31].

Several transcriptional networks that regulate antigen presentation are highly dependent on nucleocytoplasmic trafficking. Interferon-induced signaling pathways, particularly those involving STAT1 and IRF1, are essential for the induction of genes encoding MHC-I heavy chains, β2-microglobulin, transporter associated with antigen processing (TAP) proteins, and immunoproteasome subunits. Sustained nuclear localization of these transcription factors is required for effective transcriptional activation, whereas disruption of nucleo-cytoplasmic balance may limit the duration and magnitude of antigen-presenting programs [32,33].

XPO1-mediated trafficking regulates components of the nuclear factor-kappa B (NF-kB) pathway, interferon-responsive transcription factors, and several tumor suppressors that collectively influence cellular responses to immune stimulation. Aberrant XPO1 activity may therefore contribute to the attenuation of pathways required for optimal immune recognition [8,34]. Mechanistic studies have demonstrated that intracellular trafficking pathways are essential for STING activation and interferon production, whereas disruption of these processes impairs innate immune signaling and antitumor immunity.

Among the molecules potentially involved, STAT1 and IRF1 represent the most biologically plausible candidates because their nuclear localization is required for transcription of genes involved in antigen processing and MHC-I expression. However, direct evidence demonstrating altered XPO1-dependent trafficking of these factors as a cause of defective antigen presentation in MM is currently lacking. Most available evidence derives from broader immunological studies and from tumor models other than MM.

Antigen presentation is also tightly linked to intracellular protein homeostasis. The generation of antigenic peptides relies on coordinated protein degradation through the ubiquitin-proteasome system, followed by peptide transport and loading onto MHC-I complexes. Alterations in nucleocytoplasmic trafficking may modify the repertoire of peptides available for presentation, potentially affecting both antigen diversity and the quality of antitumor T-cell responses [35].

Dendritic cells in MM exhibit substantial functional abnormalities, including defective maturation, impaired cytokine production, and reduced T-cell stimulatory capacity. These alterations contribute to the establishment of an immunosuppressive marrow niche and are increasingly recognized as important drivers of immune escape. The activation of dendritic cells requires nuclear accumulation of transcription factors downstream of Toll-like receptors and interferon signaling cascades. Perturbations in nucleocytoplasmic trafficking may therefore compromise cross-presentation and limit effective priming of tumor-specific T cells [36,37].

Furthermore, impaired antigen presentation should not be viewed as an isolated event but rather as part of a broader immune-evasion program. Reduced expression of antigen-processing machinery, diminished responsiveness to interferon signaling, defective

dendritic-cell function, and progressive T-cell dysfunction cooperate to decrease tumor visibility despite the persistence of potentially immunogenic tumor-derived antigens [31,38].

Understanding how XPO1-dependent trafficking shapes antigen presentation may therefore provide important insights into the development of combination strategies aimed at restoring antitumor immunity and enhancing the activity of emerging immunotherapies in MM.

5. Nuclear Export and Innate Immune Sensing

The capacity of the immune system to detect malignant transformation relies not only on adaptive immune responses but also on the activation of intrinsic cellular surveillance pathways that recognize danger-associated molecular patterns generated during oncogenesis. Among these mechanisms, the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway has emerged as a central mediator linking genomic instability to antitumor immunity. Cytosolic DNA originating from chromosomal missegregation, micronuclei rupture, replication stress, or treatment-induced DNA damage is sensed by cGAS, resulting in the production of cyclic GMP-AMP (cGAMP), which subsequently activates STING and initiates a type I interferon response. Through this mechanism, cells can convert genomic stress into immunological signals capable of alerting the host immune system [39–42].

Activation of the cGAS-STING pathway has profound consequences for the tumor microenvironment. Following STING engagement, downstream kinases such as TBK1 phosphorylate IRF3, promoting transcription of interferon-stimulated genes and inflammatory mediators. These signals facilitate recruitment and activation of dendritic cells, natural killer cells, and tumor-specific cytotoxic T lymphocytes, thereby promoting the development of coordinated antitumor immune responses. Experimental studies have demonstrated that impairment of STING signaling may reduce immune recognition of transformed cells despite the presence of significant genomic damage, highlighting the importance of innate immune sensing in cancer control [43–46].

The effectiveness of this pathway is highly dependent on intracellular trafficking processes. STING activation is not a static molecular event but requires regulated translocation between intracellular compartments, including the endoplasmic reticulum, Golgi apparatus, and endosomal structures. These trafficking events are essential for signal propagation and for the activation of downstream transcriptional programs. Disruption of intracellular transport mechanisms can therefore attenuate interferon production, alter cytokine secretion profiles, and weaken the capacity of damaged cells to initiate immune-stimulatory responses. Emerging evidence indicates that nucleocytoplasmic transport machinery contributes indirectly to these regulatory circuits by controlling the localization of transcription factors and signaling molecules required for innate immune activation [47–49]. XPO1 inhibition has been shown to restore antigen presentation in several tumor models, whereas direct evidence in multiple myeloma remains limited. Importantly, STING trafficking primarily occurs between the endoplasmic reticulum, Golgi apparatus, and endosomal compartments and should not be interpreted as evidence of direct XPO1-mediated nuclear export. The relationship between XPO1 activity and cGAS-STING signaling is currently considered indirect and likely mediated through regulation of upstream or downstream transcriptional networks.

In MM, this issue acquires particular relevance because disease progression is accompanied by increasing chromosomal complexity, structural abnormalities, and ongoing DNA damage. Under normal circumstances, such alterations would be expected to trigger potent innate immune responses. However, advanced myeloma frequently develops within an environment characterized by limited immune activation despite extensive genomic instability. This apparent paradox suggests the existence of mechanisms capable of uncou-

pling DNA damage from effective immune sensing. Although the precise contribution of XPO1-dependent pathways remains incompletely defined, dysregulated nuclear export may facilitate adaptation to chronic genomic stress by modulating the intracellular distribution of factors involved in interferon signaling, stress responses, and transcriptional regulation [50].

Consequently, the significance of nuclear export extends beyond its established role in regulating cellular proliferation and survival. By influencing signaling networks that determine whether genomic instability is translated into immunogenic or non-immunogenic outcomes, altered nucleocytoplasmic trafficking may shape the earliest stages of immune recognition. In this framework, XPO1 is positioned as a potential regulator of the interface between malignant evolution and innate immune surveillance, contributing to the establishment of a bone marrow environment in which genetically unstable plasma cells can persist despite the continuous generation of danger signals.

However, as reported above, while several studies have demonstrated that nuclear export inhibition enhances antigen-presentation pathways in different tumor types, direct evidence in multiple myeloma remains relatively scarce. Therefore, extrapolation of these findings to MM should be interpreted cautiously. Nevertheless, the preservation of MHC-related transcriptional programs and interferon signaling observed following XPO1 inhibition supports the hypothesis that similar mechanisms may contribute to improved immune recognition in MM.

6. Regulation of NF-κB and Inflammatory Signaling

Among the signaling pathways influenced by nucleocytoplasmic trafficking, the NF-κB network occupies a particularly important position in MM. Constitutive NF-κB activation has been documented in a substantial proportion of patients and contributes to plasma-cell survival, proliferation, resistance to apoptosis, and adaptation to microenvironmental stress. Both canonical and non-canonical NF-κB pathways may be activated through genetic lesions, cytokine stimulation, and interactions with stromal cells, establishing a transcriptional program that supports disease progression [51].

The activity of NF-κB is critically dependent on intracellular compartmentalization. Under physiological conditions, NF-κB dimers are retained in the cytoplasm through association with inhibitory proteins belonging to the IκB family. Following stimulation by inflammatory or stress-related signals, IκB proteins are phosphorylated and degraded, allowing NF-κB to translocate into the nucleus and activate target genes. Restoration of homeostasis requires newly synthesized IκBα to enter the nucleus, bind NF-κB, and export the complex back to the cytoplasm. This negative feedback loop depends on XPO1-mediated nuclear export and represents a fundamental mechanism controlling the duration and intensity of NF-κB activation [52,53]. Notably, the strongest experimental evidence concerns XPO1-dependent nuclear export of IκBα and NF-κB/IκBα complexes, whereas alterations in broader NF-κB transcriptional outputs following XPO1 inhibition should be considered downstream consequences rather than evidence of direct export of all pathway components.

In MM, persistent activation of NF-κB is associated with abnormal production of soluble mediators that reinforce bidirectional communication between malignant plasma cells and the bone marrow niche. NF-κB-regulated genes include cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and several chemokines involved in cellular recruitment and survival signaling. These molecules create a self-reinforcing inflammatory circuit in which stromal cells, osteoclasts, endothelial cells, and tumor cells reciprocally sustain one another. Importantly, NF-κB activity not only promotes plasma-cell growth but also shapes the local cytokine landscape that influences immune-cell behavior [54–56].

The biological consequences of chronic NF-κB signaling differ substantially from those of acute inflammatory responses. Physiological inflammation is generally transient and designed to eliminate pathogens or damaged cells. In contrast, persistent NF-κB activation generates a prolonged inflammatory state characterized by continuous production of trophic and immunomodulatory factors. Such conditions favor accumulation of suppressive myeloid populations, expansion of regulatory immune subsets, and progressive impairment of effective antitumor responses. Therefore, inflammation in MM should not be viewed simply as an indicator of immune activation; rather, it frequently reflects the establishment of a tumor-supportive ecosystem that facilitates disease persistence [40,57–59].

Within this context, XPO1-dependent trafficking assumes particular relevance because it influences the mechanisms responsible for terminating NF-κB signaling. Abnormal nuclear export may alter the balance between activation and negative feedback, prolonging transcriptional responses that would otherwise be transient. Rather than merely amplifying inflammatory activity, dysregulated trafficking appears capable of reshaping its qualitative characteristics, favoring a chronic, tumor-promoting inflammatory state [60–62]. Consequently, XPO1 can be viewed as an upstream regulator of inflammatory circuitries that contribute to maintenance of the myeloma-supportive microenvironment and, ultimately, to the persistence of immune evasion mechanisms throughout disease evolution.

7. Nucleocytoplasmic Trafficking and T-Cell Exhaustion

While XPO1 overexpression has been directly documented in malignant plasma cells, evidence linking XPO1 dysregulation to immune-cell dysfunction in MM remains considerably more limited. Therefore, the following sections distinguish observations obtained in MM models from immunological mechanisms inferred from studies performed in other malignancies or non-MM experimental systems.

7.1. T-Cell Exhaustion

T-cell exhaustion is increasingly recognized as a major determinant of immune dysfunction in MM. As the disease progresses from precursor conditions to overt and relapsed MM, persistent antigenic stimulation, chronic inflammatory signaling, and prolonged exposure to immunosuppressive factors within the bone marrow microenvironment promote the development of dysfunctional T-cell states characterized by reduced proliferative capacity, impaired cytokine secretion, diminished cytotoxicity, and sustained expression of inhibitory receptors [63,64].

The exhausted phenotype is orchestrated by a complex network of transcriptional regulators that control T-cell differentiation and fate decisions. Key molecular mediators include NFAT, TOX, members of the NR4A family, STAT proteins, BATF, and TCF1, which collectively shape exhaustion-associated transcriptional and epigenetic programs. A common feature of many of these regulators is their dependence on precise nucleocytoplasmic trafficking for activation and transcriptional activity [65–68]. Continuous shuttling between the nucleus and cytoplasm is required to coordinate responses to antigen receptor signaling, cytokine stimulation, and environmental stress, suggesting that disruption of intracellular trafficking mechanisms may substantially influence T-cell function.

Although most investigations of XPO1 biology in MM have focused on malignant plasma cells, emerging evidence suggests that nuclear export pathways also influence immune-cell fitness. Experimental studies evaluating selective inhibitors of nuclear export (SINEs) have shown that XPO1 inhibition can modulate T-cell biology and may attenuate features associated with exhaustion. In preclinical models, clinically relevant intermittent selinexor dosing preserved T-cell effector functions and maintained immune homeostasis while retaining antitumor activity, supporting the possibility of combining XPO1 inhibition

with immunotherapeutic strategies. Moreover, other preclinical observations indicate that selinexor and newer XPO1 inhibitors can preserve functional T-cell characteristics, enhance activation-associated signaling, and support the generation of more effective antitumor immune responses [69].

The bone marrow niche further amplifies these effects. Myeloma-associated stromal populations, regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages generate a cytokine milieu enriched in suppressive mediators, including IL-10 and TGF-β, that promote progressive T-cell dysfunction. Sustained signaling through these pathways induces transcriptional reprogramming that favors terminal exhaustion and loss of immune surveillance. Because many of the signaling intermediates involved in these processes depend on nuclear translocation and retention for their activity, alterations in nucleocytoplasmic trafficking may contribute to stabilizing exhaustion-associated gene-expression programs [70–72].

This concept has acquired particular relevance with the introduction of T-cell-dependent immunotherapies. Both bispecific antibodies and chimeric antigen receptor (CAR)-T cells require competent effector lymphocytes capable of sustained expansion, cytokine production, and serial target-cell killing. Clinical and translational studies increasingly indicate that the functional status of endogenous T cells before treatment significantly influences therapeutic outcomes [73,74].

Consequently, biological pathways that regulate T-cell fitness have become attractive therapeutic targets. By modulating the intracellular localization of critical transcriptional regulators and signaling molecules, nucleocytoplasmic trafficking may represent an underappreciated determinant of immune competence and responsiveness to modern immunotherapeutic approaches in neoplastic diseases.

Although XPO1 inhibition can modulate inflammatory signaling pathways implicated in T-cell exhaustion, direct reversal of exhausted T-cell phenotypes has not yet been conclusively demonstrated in MM patients. Therefore, potential effects on T-cell fitness remain speculative and warrant dedicated investigation. Moreover, although transcription factors such as NFAT, STAT proteins, TOX, and NR4A family members play central roles in exhaustion-associated programs, direct evidence linking their XPO1-dependent trafficking to T-cell exhaustion in MM remains limited.

Furthermore, while much of the current discussion focuses on the capacity of XPO1 inhibition to enhance anti-tumor immune responses, evidence suggests that its effects on immune-effector cells are not uniformly beneficial. Preclinical studies have demonstrated that prolonged or continuous XPO1 inhibition can transiently impair T-cell activation, proliferation, and cytokine production, indicating that immune cells themselves are pharmacological targets of XPO1 blockade.

These observations suggest that the immunological consequences of XPO1 inhibition are highly dependent on treatment context. Variables such as drug concentration, duration of exposure, and sequencing relative to immunotherapy may substantially influence the balance between anti-tumor activity and preservation of immune competence [69]. Importantly, transient suppression of T-cell activation does not necessarily preclude therapeutic benefit if adequate recovery periods are incorporated into treatment schedules.

Consequently, optimization of dosing strategies may represent a critical determinant of success for combinations involving selinexor and immune-based therapies. Rather than viewing XPO1 inhibition as intrinsically immunostimulatory or immunosuppressive, current evidence supports a model in which its net immunological effect emerges from the dynamic interaction between tumor cells, immune-effector populations, and treatment timing.

7.2. Nucleocytoplasmic Trafficking and Natural Killer Cell Dysfunction

Natural killer (NK) cells constitute a critical component of immune surveillance in MM, providing rapid antitumor responses independently of antigen presentation and MHC restriction. The importance of NK-cell activity in MM is highlighted by the clinical efficacy of therapeutic antibodies that rely on antibody-dependent cellular cytotoxicity (ADCC), including anti-CD38 and anti-SLAMF7 monoclonal antibodies [75]. However, disease progression is frequently accompanied by quantitative and qualitative alterations of NK-cell populations, resulting in impaired cytotoxicity, defective cytokine production, and reduced capacity to eliminate malignant plasma cells. These abnormalities contribute substantially to immune escape and may limit the effectiveness of modern immunotherapeutic approaches [76,77].

NK-cell activation is regulated by a complex balance between activating and inhibitory receptors, including NKG2D, DNAM-1, NKp30, NKp44, NKp46, TIGIT, and various killer immunoglobulin-like receptors (KIRs). Signaling downstream of these receptors ultimately converges on transcriptional programs requiring the coordinated activity and intracellular trafficking of transcription factors such as NF-κB, STAT family members, AP-1, and FOXO proteins [78].

Because many of these regulators are influenced directly or indirectly by nucleocytoplasmic transport systems, dysregulated XPO1 activity may affect NK-cell functionality through alterations in signaling dynamics rather than through changes in gene expression alone.

An important distinction should be made between restoration of NK-cell function and increased susceptibility of malignant cells to NK-cell-mediated cytotoxicity. Several studies suggest that XPO1 inhibition may primarily act through tumor-cell-intrinsic mechanisms that enhance immune recognition rather than directly reversing NK-cell dysfunction. In particular, modulation of antigen-presentation and immune-evasion pathways may alter the balance between activating and inhibitory signals perceived by NK cells. Experimental evidence from chronic lymphocytic leukemia (CLL) cell lines and primary CLL samples demonstrated that selinexor-induced XPO1 inhibition downregulated HLA-E expression on malignant B cells, thereby enhancing NK-cell activation and cytotoxicity through reduced engagement of the inhibitory receptor NKG2A [76]. Importantly, these observations were obtained in CLL models rather than in multiple myeloma, and direct confirmation in MM remains unavailable. These findings indicate that XPO1 blockade may facilitate NK-cell antitumor activity by reducing mechanisms of tumor immune escape, although such effects should not be interpreted as direct restoration of NK-cell fitness.

By contrast, direct NK-cell restoration would require evidence of improved NK-cell proliferation, cytokine production, cytotoxic granule release, metabolic fitness, or reversal of exhaustion phenotypes. At present, the available evidence supporting these NK-cell-intrinsic effects remains more limited than that supporting enhanced tumor susceptibility to NK-cell attack. Consequently, the immunological benefits of XPO1 inhibition likely derive from a combination of tumor-cell sensitization and, potentially, partial recovery of NK-cell effector functions, with the relative contribution of each mechanism varying across disease contexts.

An additional mechanism linking XPO1 to NK-cell biology involves interferon signaling. Type I and type II interferons play essential roles in NK-cell activation, survival, metabolic fitness, and cytotoxic effector function. Sustained nuclear localization of STAT1 and other interferon-responsive transcription factors is required for optimal transcriptional responses, whereas excessive nuclear export may shorten transcriptional activity and attenuate the expression of genes involved in cytotoxicity and immune surveillance [4,79]. Consequently, aberrant nucleocytoplasmic trafficking may contribute to the progressive decline in NK-cell competence characteristic of advanced MM.

The bone marrow microenvironment further amplifies NK-cell dysfunction. Elevated levels of TGF-β, IL-10, and other suppressive mediators inhibit NK-cell activation while promoting the accumulation of regulatory myeloid populations. Since these cytokine-driven pathways depend on tightly regulated nucleocytoplasmic signaling events, alterations in XPO1-dependent trafficking may indirectly reinforce immunosuppressive circuits that limit NK-cell activity. In this context, dysregulated nuclear export may contribute simultaneously to tumor-cell survival and to the suppression of innate immune effector mechanisms [30,72,78]. Emerging evidence from studies of SINEs suggests that XPO1 inhibition may exert immunomodulatory effects extending beyond malignant plasma cells. Although available data remain limited, restoration of appropriate intracellular localization of immune-regulatory proteins has been associated with enhanced antitumor immune responses and improved immune-cell functionality in preclinical models [80]. These observations raise the possibility that XPO1 inhibition could partially restore NK-cell competence, thereby enhancing both endogenous immune surveillance and the efficacy of antibody-based therapies that depend on NK-cell-mediated cytotoxicity.

7.3. XPO1, Myeloid-Derived Suppressor Cells, and Macrophage Reprogramming

Beyond lymphocyte dysfunction, immune escape in MM is strongly influenced by the accumulation and functional reprogramming of myeloid populations within the bone marrow microenvironment. MDSCs and tumor-associated macrophages contribute to immune evasion through suppression of T-cell responses, production of immunomodulatory cytokines, promotion of angiogenesis, and support of malignant plasma-cell survival.

XPO1-dependent nuclear export may influence several signaling pathways involved in myeloid-cell activation and polarization. In particular, XPO1 regulates the intracellular trafficking of proteins linked to NF-κB signaling, inflammatory transcriptional programs, and cytokine production. Given the central role of NF-κB in macrophage activation and MDSC expansion, dysregulated nuclear export may indirectly contribute to the establishment of an immunosuppressive myeloid compartment.

In MM, elevated levels of MDSCs have been associated with disease progression, T-cell dysfunction, and resistance to immune-mediated tumor control. Although direct studies investigating XPO1 activity in MDSCs remain limited, inhibition of XPO1 has been shown to attenuate pro-inflammatory and survival pathways that sustain tumor-promoting myeloid populations in several experimental systems.

More direct mechanistic evidence linking XPO1 activity to myeloid-cell-mediated immunosuppression has recently been provided by Daneshmandi et al. In murine tumor models and complementary functional studies, the authors demonstrated that XPO1 regulates the nuclear export of ERK1/2 in MDSCs. Pharmacological inhibition of XPO1 resulted in nuclear retention of ERK1/2, impaired suppressive activity of MDSCs, and enhancement of antitumor immune responses. These findings suggest that XPO1-dependent trafficking is not merely associated with myeloid-cell expansion but may directly regulate key signaling pathways governing MDSC-mediated immune suppression. Although these observations were not generated in multiple myeloma models, they provide one of the strongest mechanistic links between nuclear export and immune evasion currently available [81].

Similarly, macrophage polarization appears to be influenced by pathways regulated by nuclear export. Tumor-associated macrophages often display an M2-like phenotype characterized by immunosuppressive activity, secretion of IL-10 and TGF-β, promotion of angiogenesis, and support of tumor growth. Through modulation of NF-κB and other transcriptional regulators, XPO1 inhibition may favor a shift toward a more inflammatory and antitumor macrophage state, although definitive evidence in multiple myeloma is still lacking.

Collectively, these observations suggest that the immunological effects of XPO1 inhibition may extend beyond direct actions on malignant plasma cells and lymphocyte populations. Remodeling of the myeloid compartment could represent an additional mechanism through which nuclear export inhibition restores immune surveillance. Nevertheless, dedicated mechanistic studies are needed to clarify the specific roles of MDSCs and macrophages in mediating the immunomodulatory activity of XPO1-targeted therapies in multiple myeloma.

8. A Conceptual Framework Linking Nuclear Export and Immune Escape

Several observations support the hypothesis that dysregulated nucleocytoplasmic trafficking may function as an upstream regulatory framework linking multiple mechanisms of immune escape in MM. However, current evidence remains insufficient to definitively classify this process as a distinct hallmark of myeloma biology.

Nucleocytoplasmic trafficking regulates multiple biological systems that have independently been implicated in immune evasion. XPO1 controls the intracellular localization of numerous tumor suppressors, transcription factors, and signaling molecules. These pathways influence not only tumor-cell survival but also processes directly relevant to immune recognition, including cytokine production, inflammatory responses, cellular stress adaptation, and communication between malignant plasma cells and immune-cell populations [82,83]. Consequently, abnormalities in nuclear export have the potential to affect several immunological circuits simultaneously rather than acting through a single downstream mechanism.

A further characteristic is its ability to operate across multiple cellular compartments of the tumor ecosystem. The broad distribution of these effects distinguishes nucleocytoplasmic trafficking from many conventional oncogenic pathways and suggests a systems-level role in coordinating immune responses throughout the myeloma niche. Perhaps the strongest argument for considering dysregulated nuclear export as an organizing principle of immune escape is its upstream regulatory position. Rather than constituting a discrete signaling pathway, it establishes the spatial architecture through which multiple immune programs are coordinated.

Emerging data support the possibility that restoration of appropriate intracellular protein localization may reactivate several complementary layers of immune surveillance simultaneously [84]. The available evidence raises the possibility that dysregulated nucleocytoplasmic trafficking contributes to immune-evasion-related processes beyond its tumor-cell intrinsic functions.

Nevertheless, further experimental and clinical validation is required before its role can be considered firmly established.

By coordinating molecular networks that govern immune recognition, inflammatory signaling, cellular stress responses, and immune-cell function, aberrant nuclear export may constitute a central and previously underrecognized mechanism driving immune escape in MM (Table 1). This perspective provides a unifying conceptual model linking tumor biology with immunological dysfunction and offers a rationale for the continued development of nuclear export-targeted therapeutic strategies.

Table 1. Principal biological pathways potentially influenced by XPO1-dependent nuclear export and their proposed relevance to immune escape in multiple myeloma. Dysregulated nucleocytoplasmic trafficking affects tumor suppressor activity, antigen presentation, innate immune sensing, inflammatory signaling, T-cell functionality, myeloid-cell polarization, and microenvironmental adaptation, collectively promoting immune evasion and disease persistence. Evidence supporting these immune-cell-specific mechanisms is derived partly from non-MM experimental systems and therefore should be interpreted as hypothesis-generating until validated in MM.

Biological Process	Representative Molecules/Pathways	Consequence of Dysregulated Nuclear Export	Potential Impact on Immune Escape	Ref.
Tumor suppressor regulation	p53, p21, p27, FOXO proteins, RB1	Reduced nuclear tumor-suppressive activity	Enhanced survival of malignant plasma cells	[12,14,22]
Antigen presentation	STAT1, IRF1, MHC-I regulatory pathways	Reduced antigen-processing/presentation machinery	Decreased recognition by cytotoxic T cells	[32–35]
Innate immune sensing	cGAS-STING, TBK1, IRF3	Potential modulation of interferon-related signaling pathways	Reduced recruitment of immune effectors	[39–42]
Inflammatory signaling	NF-kB/IkB axis	Sustained cytokine and chemokine production	Tumor-promoting inflammatory milieu	[52,53,57,59]
T-cell functionality	NFAT, TOX, NR4A, STAT proteins	Putative exhaustion-associated programs	Impaired antitumor T-cell responses	[69–72]
Myeloid remodeling	Macrophage and MDSC pathways	Potential expansion of suppressive populations	Reduced immune surveillance	[81]
Microenvironment adaptation	Cytokines, adhesion molecules, stromal interactions	Strengthened bone marrow niche	Persistence of immune-permissive conditions	[29]

In conclusion, a distinctive aspect emerging from the available literature is that nucleocytoplasmic trafficking may act as an upstream regulatory node coordinating multiple immune-evasion pathways that are otherwise considered separately. Rather than representing an independent immune mechanism, XPO1-dependent trafficking may influence antigen presentation, inflammatory signaling, innate immune sensing, myeloid-cell polarization, T-cell fitness, and responsiveness to immunotherapy through shared transport-dependent regulatory circuits. Although many of these connections remain incompletely validated in multiple myeloma, this framework highlights specific mechanistic hypotheses that can be experimentally tested and may help explain how diverse immune-escape programs converge during disease progression

9. Therapeutic Implications

The recognition of XPO1 as a central regulator of malignant cell biology has led to the development of SINE compounds, a novel therapeutic class specifically designed to disrupt XPO1-mediated transport [85,86]. Clinical trials have demonstrated meaningful activity in patients with relapsed or refractory disease, including heavily pretreated populations exposed to proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies. These findings culminated in regulatory approval of selinexor-containing regimens and established nuclear export inhibition as a clinically actionable vulnerability in MM [87].

Rather than functioning exclusively as antitumor agents, SINE compounds may act as biological modulators capable of reshaping interactions between tumor cells and immune effectors [8].

An important consideration is that the immunological consequences of XPO1 inhibition are likely to depend on treatment intensity, duration, and scheduling. While transient inhibition of nuclear export may enhance immune surveillance by restoring antitumor signaling pathways and reducing tumor-associated immunosuppression, prolonged or excessive blockade could theoretically impair physiological functions of normal immune cells that also rely on tightly regulated nucleocytoplasmic trafficking. Preclinical evidence suggests that clinically relevant intermittent dosing schedules may preserve immune homeostasis while maintaining antitumor activity. These observations raise the possibility that treatment timing and sequencing may be critical determinants of clinical benefit. For example, short-term XPO1 inhibition administered before T-cell-engaging therapies or cellular immunotherapies could potentially optimize the tumor microenvironment and improve immune-cell fitness while minimizing undesirable effects on effector-cell function. Consequently, future studies should not only evaluate combination partners but also define the optimal dose, duration, and sequencing of XPO1-targeted therapies in immunotherapy-based treatment strategies.

This concept is particularly relevant in the era of immune-based therapies. The clinical management of MM has undergone a profound transformation with the introduction of T-cell-engaging bispecific antibodies, CAR T-cell therapies, and next-generation cereblon E3 ligase modulators. Despite remarkable response rates, a significant proportion of patients eventually experience disease progression, often accompanied by evidence of immune dysfunction, impaired effector-cell persistence, or microenvironmental adaptation. Consequently, strategies capable of improving the quality of antitumor immune responses have become an area of intense investigation [88].

Among potential combination strategies, integration with monoclonal antibodies represents one of the most immediately translatable opportunities. Preclinical and clinical data have demonstrated encouraging activity when selinexor is combined with anti-CD38-based regimens, proteasome inhibitors, and immunomodulatory drugs [89–91]. Importantly, immunomodulatory agents exert broad effects on T cells, NK cells, and cytokine production through degradation of transcription factors such as Ikaros and Aiolos. The mechanistic complementarity between cereblon-directed therapies and XPO1 inhibition raises the possibility of simultaneously targeting intracellular survival pathways and immune-regulatory programs, thereby improving therapeutic depth and durability.

An even more intriguing possibility concerns the integration of XPO1 inhibitors with cellular immunotherapies. The success of BCMA-directed CAR-T cells has highlighted the critical importance of T-cell fitness and microenvironmental context in determining long-term outcomes. Because nuclear export pathways influence multiple signaling networks involved in cellular stress adaptation and inflammatory regulation, transient administration of an XPO1 inhibitor before or during cellular therapy could theoretically create a more favorable immunological landscape. The timing of exposure may be particularly important in this setting. Continuous XPO1 inhibition during prolonged immune activation could potentially affect immune-cell function, whereas transient exposure before CAR-T-cell infusion or bispecific-antibody treatment may provide immune conditioning benefits while preserving effector-cell activity. Such an approach might enhance immune-cell functionality, increase tumor susceptibility to cytotoxic attack, or reduce microenvironment-mediated resistance [92]. While these hypotheses remain under active investigation, they provide a compelling framework for future translational studies.

XPO1 Inhibition and the BCMA Axis

B-cell maturation antigen (BCMA) has emerged as the dominant immunotherapeutic target in multiple myeloma and constitutes the backbone of several highly effective therapeutic strategies, including antibody-drug conjugates, bispecific antibodies, and, as reported above, CAR T-cell therapies [93]. Despite remarkable clinical activity, resistance to BCMA-directed treatments remains a major challenge and may arise through multiple mechanisms, including antigen downregulation, clonal selection, T-cell dysfunction, and adaptation of the bone marrow microenvironment [81,94].

The relationship between XPO1 inhibition and BCMA-directed immunotherapies may be supported by more direct evidence than previously appreciated. In a translational study, Wang et al. demonstrated that selinexor pretreatment enhanced the activity of anti-BCMA CAR-T cells against myeloma cell lines and was associated with changes in BCMA surface expression. Importantly, the authors reported an increase in the proportion of BCMA-positive tumor cells rather than a uniform increase in BCMA expression intensity on individual cells. This distinction may be biologically relevant because expansion of the BCMA-positive fraction could increase the number of targetable tumor cells even when per-cell antigen density changes only modestly [95].

Beyond antigen expression, selinexor-pretreated myeloma cells exhibited greater susceptibility to CAR-T-cell-mediated cytotoxicity, suggesting that XPO1 inhibition may influence additional determinants of immune recognition and tumor-cell vulnerability. These observations are consistent with the broader hypothesis that nucleocytoplasmic trafficking regulates pathways involved in tumor immunogenicity and responsiveness to immune-mediated killing.

The same report also described two patients with relapsed/refractory extramedullary multiple myeloma who received a sequential strategy incorporating selinexor and anti-BCMA CAR-T-cell therapy and achieved encouraging clinical responses. However, these clinical observations should be interpreted cautiously because they derive from a very limited number of cases without a comparator arm. Therefore, although the findings support the biological rationale for combining XPO1 inhibition with BCMA-targeted therapies, they should currently be regarded as hypothesis-generating rather than definitive clinical evidence (Table 2).

Table 2. Current and emerging therapeutic strategies based on XPO1 inhibition in multiple myeloma. The table summarizes the biological rationale, potential immunological consequences, and current stage of clinical development of approaches integrating selective inhibitors of nuclear export with proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, bispecific antibodies, and cellular immunotherapies.

Regimen	Clinical Setting	Regulatory/Clinical Status	Relevance to Immune Framework	Ref.
Selinexor + Dexamethasone	Triple-class refractory MM	Approved historical indication	Clinical efficacy demonstrated; immune mechanism not directly established	[85]
Selinexor + Bortezomib + Dexamethasone	Relapsed/Refractory MM	Regulatory approval based on BOSTON trial	Clinical benefit documented; contribution of immune modulation remains uncertain	[19,87,90]
Other selinexor-based combinations	Various RRMM settings	Ongoing clinical evaluation	Immunologic effects remain under investigation	[87,89,91,92,96]

Collectively, these data suggest that XPO1 inhibition may enhance BCMA-directed immunotherapy through multiple mechanisms, including expansion of the targetable

BCMA-positive tumor-cell population and increased sensitivity to CAR-T-cell-mediated killing. Further prospective studies are required to determine the magnitude and clinical relevance of these effects.

10. Conclusions and Future Perspectives

Immune escape is increasingly recognized as a dynamic and multifactorial process that evolves throughout the natural history of MM. While considerable attention has been devoted to individual mechanisms such as T-cell dysfunction, expansion of suppressive myeloid populations, and altered antigen presentation, the upstream regulatory systems coordinating these phenomena have remained less clearly defined [96,97].

In this review, we propose that dysregulated nucleocytoplasmic trafficking, particularly XPO1-dependent nuclear export, may represent an overarching regulatory framework capable of integrating several mechanisms involved in tumor progression and immune evasion. Importantly, while XPO1-dependent nuclear export is an established biological process in multiple myeloma, many of the immune-regulatory effects discussed in this review are supported by indirect evidence, observations from non-myeloma systems, or preclinical studies. Therefore, the proposed model should be interpreted primarily as a hypothesis-generating framework requiring dedicated mechanistic validation.

By influencing the intracellular localization of proteins involved in stress adaptation, transcriptional regulation, inflammatory signaling, and immune communication, nuclear export may contribute to how malignant plasma cells interact with their microenvironment (Table 3).

Nevertheless, several limitations should be acknowledged. First, much of the available evidence regarding the immunological consequences of XPO1 dysregulation derives from preclinical studies, whereas direct mechanistic data obtained from patient-derived samples remain comparatively limited. Second, many investigations have focused on the tumor-intrinsic effects of XPO1 inhibition, while its broader impact on immune and stromal compartments of the bone marrow ecosystem is still incompletely characterized.

Among the studies linking XPO1 activity to immune suppression, one of the most mechanistically informative investigations demonstrated that XPO1-dependent nuclear export regulates the intracellular localization of ERK1/2, thereby influencing the immunosuppressive activity of MDSCs [81]. Mechanistic support for this framework is provided by the recently described XPO1-ERK1/2-MDSC axis, discussed above, which demonstrates that nucleocytoplasmic trafficking can directly regulate myeloid-cell-mediated immune suppression [81]. Hao et al. subsequently discussed and contextualized these findings [98].

However, the relevance of these observations to MM remains to be established. The study was not specifically performed in myeloma models, and the phenotypic and functional heterogeneity of MDSCs across tumor types may limit direct extrapolation. Nevertheless, this work supports the hypothesis that XPO1 inhibition may influence immune escape not only through effects on malignant plasma cells but also through modulation of immunosuppressive myeloid populations.

Third, the pleiotropic nature of nuclear export makes it challenging to distinguish primary effects from secondary downstream consequences, particularly in complex cellular networks where multiple signaling pathways converge. As a result, the precise contribution of altered nucleocytoplasmic trafficking to specific immune escape mechanisms remains to be fully elucidated.

Furthermore, although XPO1 inhibition may restore antitumor immunity, prolonged or excessive blockade of nuclear export could theoretically interfere with physiological immune-cell functions. The balance between immune activation and immune impairment remains insufficiently characterized. Another important limitation of the current conceptual

framework is that some proposed links between XPO1 inhibition and immune reprogramming are supported by indirect evidence from other malignancies or non-MM experimental systems. Future mechanistic studies specifically conducted in MM will be essential to validate these hypotheses and define their clinical relevance. Finally, no validated biomarkers currently identify those patients in whom immune escape is preferentially driven by XPO1-dependent mechanisms.

Table 3. Advanced experimental and molecular platforms that may facilitate future investigation of XPO1-driven immune escape in multiple myeloma. These technologies enable high-resolution characterization of tumor heterogeneity, immune-cell states, spatial organization of the bone marrow niche, and functional interactions between malignant plasma cells and the microenvironment, thereby supporting biomarker discovery and development of next-generation therapeutic strategies.

Technology	Main Application in MM	Potential Contribution to XPO1 Research	Expected Translational Impact	Ref.
Single-cell RNA sequencing (scRNA-seq)	Characterization of tumor and immune heterogeneity	Identification of cell-specific XPO1-dependent transcriptional programs	Biomarker discovery and patient stratification	[99,100]
Single-cell ATAC-seq	Chromatin accessibility profiling	Definition of epigenetic consequences of altered nuclear export	Identification of resistance mechanisms	[99,100]
Spatial transcriptomics	Mapping cellular interactions in situ	Localization of XPO1-driven immune-escape niches	Microenvironment-guided therapeutic strategies	[101]
Mass cytometry (CyTOF)	High-dimensional immune profiling	Quantification of immune-cell states affected by XPO1 activity	Monitoring of immunological responses	[99,100]
Multi-omics integration	Combined genomic, transcriptomic and proteomic analysis	Reconstruction of XPO1-centered regulatory networks	Precision medicine approaches	[102]
3D bone marrow organoids	Modeling tumor-microenvironment interactions	Evaluation of XPO1 effects in physiologically relevant systems	Improved preclinical prediction	[103,104]
Bone marrow-on-a-chip platforms	Dynamic modeling of marrow architecture and flow	Study of immune-cell trafficking and drug responses	Optimization of therapeutic combinations	[103]
Patient-derived co-culture systems	Functional validation using primary cells	Assessment of immune and stromal responses to XPO1 inhibition	Translational validation of experimental findings	[103]

Future research should therefore move beyond conventional bulk analyses and adopt technologies capable of resolving cellular heterogeneity at unprecedented resolution. Single-cell RNA sequencing, single-cell ATAC-sequencing, spatial transcriptomics, multiplex imaging, and mass cytometry now permit simultaneous evaluation of tumor cells and immune populations within their native microenvironment [99–101].

Application of these approaches could identify cell-type-specific nuclear export programs, reveal previously unrecognized interactions between plasma cells and immune subsets, and define biomarkers predictive of response to XPO1-targeted therapies. Integration of transcriptomic, epigenomic, and proteomic datasets through multi-omics platforms may further clarify how nuclear export influences complex regulatory networks operating across distinct cellular compartments [102].

Equally important will be the development of experimental models that more faithfully recapitulate the architecture of the myeloma niche. Traditional two-dimensional cultures fail to reproduce the spatial organization, cell–cell interactions, and cytokine gradients characteristic of the bone marrow environment. Recent advances in three-dimensional culture systems, organoids, biomaterial-based scaffolds, microfluidic platforms, and bone marrow-on-a-chip technologies provide opportunities to study nucleocytoplasmic trafficking in physiologically relevant settings [103,104]]. These models may prove particularly valuable for investigating how XPO1 modulation affects immune-cell recruitment, cellular crosstalk, therapeutic resistance, and responses to immunotherapies under conditions that closely resemble human disease.

Another priority will be the integration of nuclear export inhibition with emerging immunotherapeutic strategies. Future studies should determine whether XPO1 inhibition can enhance immune-cell persistence, improve functional fitness of effector populations, or augment sensitivity of malignant plasma cells to immune-mediated killing [103]. Such investigations may identify optimal sequencing strategies and facilitate the development of rational combination regimens.

In conclusion, the concept of nucleocytoplasmic trafficking as a potential regulator of immune escape provides a unifying hypothesis connecting tumor-cell biology with microenvironmental and immunological processes. However, many of the proposed mechanistic links reviewed here remain incompletely validated in myeloma-specific experimental systems and should therefore be regarded as testable hypotheses rather than established biological mechanisms. While existing evidence is compelling, substantial mechanistic and translational work remains necessary before this model can be considered definitively established in multiple myeloma.

Continued investigation using advanced molecular profiling technologies and next-generation three-dimensional disease models will be essential to validate this hypothesis and to translate these biological insights into clinically meaningful therapeutic innovations. Ultimately, a deeper understanding of nuclear export biology may reveal novel opportunities to restore durable immune control in multiple myeloma.

Author Contributions: Conceptualization, A.A., S.G. and M.D.G.; methodology, F.S., A.B., M.F. and S.R.; writing—original draft preparation, D.G., M.D.G., S.G., A.B., M.F. and S.R.; writing—review and editing, A.A.; supervision, A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

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

Acknowledgments: During the preparation of this work, the authors used ChatGPT-6 (OpenAI) to improve the language, clarity, and readability of the manuscript and to assist in the preparation and graphical design of figures. After using this tool, the authors reviewed and edited the content and figures as needed and take full responsibility for the content of the published article.

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

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