onco

Editorial

Targeting of Tumor Dormancy Pathways: An Editorial to the Special Issue

Constantin N. Baxevanis [1,2,*] and Angelos D. Gritzapis [1]

[1] Cancer Immunology and Immunotherapy Center, Saint Savas Cancer Hospital, 171 Alexandras Avenue, 11522 Athens, Greece; agkritzapis@agsavvas-hosp.gr
[2] Flow Cytometry Unit, Department of Biology, National and Kapodistrian University of Athens, Panepistimiopolis, Ilissia, 15784 Athens, Greece
* Correspondence: costas.baxevanis@gmail.com or cnbaxevanis@biol.uoa.gr; Tel.: +30-210-6409380 or +30-210-7274174

1. Introduction

A central obstacle in contemporary oncology is tumor relapse and metastatic recurrence. Metastatic recurrence denotes the reappearance of cancer in distant tissues months, years, or even decades after apparent eradication of the primary lesion, and it remains the leading cause of cancer-related mortality [1]. The ability of malignant cells to enter prolonged periods of dormancy resembles a conserved physiological program observed in cell types such as memory T lymphocytes [2,3]. To persist through chemotherapy, dormant tumor cells must adopt distinct biological features relative to healthy cells, including resistance to stress and cytotoxic drugs, invasive and disseminative capabilities, and the ability to both enter and exit dormancy. Mechanistically, dormancy is an active survival program that allows cells to avoid apoptosis under stress (chemotherapy, nutrient/oxygen deprivation, and immune attack) by switching signaling and metabolic states. Key pathways that determine whether a disseminated cancer cell dies or becomes dormant include ERK/p38 signaling balance (low ERK–high p38 favors dormancy), pro-survival autophagy and stress-response programs, and niche-derived cues (extracellular-matrix, TGF-β, integrin signaling, and transcriptional regulators such as NR2F1) [4,5]. These pathways suppress proliferation while maintaining viability and resistance to apoptosis, thus prolonging tumor dormancy and hindering relapses. Indeed, although apoptosis remains a central aim of anticancer therapies because it effectively reduces tumor burden, this therapeutic virtue is complicated by the induction of compensatory proliferation, tumor repopulation, and the emergence of acquired resistance, phenomena that call into question an exclusive reliance on pro-apoptotic approaches [6]. Injured tumor tissue mounts active defensive responses (including therapy-induced senescence and a senescence-associated secretory phenotype, plus inflammation and repair programs), revealing inherent limits to strategies that simply "wound" the cancer [7]. In this sense, apoptosis can act as a double-edged sword: it produces early therapeutic gains that may later facilitate relapse, for example, caspase-3–dependent signals from dying cells stimulate the proliferation of surviving tumor cells, and clinically accelerated repopulation after cytotoxic radiotherapy has long been documented [8]. Although inhibiting anti-apoptotic proteins (e.g., BCL-2 family members) often sensitizes cancer cells in preclinical and translational models, clinical trials of BCL-2/BH3-mimetic strategies in solid malignancies have produced inconsistent results, implying that additional microenvironmental and adaptive factors determine ultimate outcome [9].

check for updates

Received: 13 October 2025
Revised: 24 October 2025
Accepted: 27 October 2025
Published: 3 November 2025

Citation: Baxevanis, C.N.; Gritzapis, A.D. Targeting of Tumor Dormancy Pathways: An Editorial to the Special Issue. *Onco* **2025**, *5*, 48. https://doi.org/10.3390/onco5040048

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

All of these studies provide a nuanced perspective on tumor cell behavior, underscoring that signals emitted by dying cells may facilitate the survival of neighboring cells; in comparison, rapidly proliferating cells may actively promote the elimination of adjacent competitors. Alternatively, it is reasonable to propose that tumors behave as miniature evolutionary ecosystems as Darwinian "survival of the fittest" operates within a heterogeneous cell population so that both rapid proliferation and alternative, low-activity strategies can be selectively favored [10,11]. Highly proliferative clones may actively displace or eliminate neighbors (for example, via cell-in-cell processes such as entosis), whereas other cells adopt a stress-resistant, quiescent strategy that preserves long-term survival under hostile conditions [12]. Mechanistically, dying tumor cells feed this dynamic process since (i) apoptotic execution (caspase-3 activity) can generate proliferative mediators (notably a COX-2/PGE2 axis) that stimulate repopulation; (ii) dying cells release "find-me"/"eat-me" signals whose efferocytic clearance programs macrophages toward immunoregulatory, pro-repair phenotypes; and (iii) apoptotic bodies/extracellular vesicles transfer bioactive cargo to neighbors, all of which are sensed by surviving cells and the stroma to remodel the niche [8]. These extracellular inputs are interpreted via intracellular circuity (for example, ERK/p38 MAPK balance and dormancy transcriptional nodes such as NR2F1), tipping individual cells toward durable quiescence or renewed proliferation; together, death-derived signaling and competitive elimination are therefore complementary evolutionary forces that shape relapse and therapeutic resistance [13].

Tumor dormancy, driven by adaptive signaling and niche-derived survival programs, underlies metastatic recurrence and limits the long-term efficacy of apoptosis-focused therapies. Because cytotoxic approaches can paradoxically promote repopulation and resistance, durable cancer control will require strategies that target the survival and reactivation mechanisms of dormant cells, including metabolic, autophagic, and microenvironmental cues, and combine them with immune- or dormancy-disrupting interventions alongside sustained surveillance. The articles included in our Special Issue present current insights into tumor dormancy, identify candidate targets within dormancy pathways, and explore translational prospects for leveraging dormancy to improve cancer treatment.

2. The Current State of the Knowledge in Tumor Dormancy, Targeting of Tumor Dormancy Pathways, and Future Prospects for Exploiting Tumor Dormancy for Cancer Therapies

In his commentary, Razwik Mirzayans [14] notes that divergent outcomes following apoptosis or other regulated forms of cell death during treatment contribute both to interpatient variability and to intratumoral heterogeneity. Rather than dying, some cancer cells enter a long-lived but often reversible dormant state, frequently induced by therapy, for example, via therapy-induced senescence. The principal drivers of dormancy reversal in solid tumors and tumor-derived cell lines include therapy-induced alterations of the immune microenvironment that erode immunosurveillance, together with epigenetic and transcriptional reprogramming that confers stem-like properties. Mirzayans also emphasizes that recovery can occur not only before caspase activation but even after later apoptotic events such as mitochondrial fragmentation, chromatin condensation, cell shrinkage, and the formation of apoptotic bodies. This return-from-death phenomenon, termed anastasis ("rising to life"), can produce progeny with increased micronuclei and chromosomal instability, thereby elevating aneuploidy and promoting aggressive disease. Mirzayans further proposes that inducing dormancy may be preferable to forcing widespread apoptosis: moderate drug doses that promote dormancy (for instance, by inducing senescence) are likely to cause fewer adverse effects, such as severe immunosuppression, than the high doses often required to trigger massive apoptosis. Because dormancy is a common consequence

of standard treatments, some groups have proposed a two-step plan: drive tumor cells into a senescent /dormant state and then administer senolytics to clear them. Such measures would imply that, in acquiring therapy resistance, cancer cells co-opt homeostatic mechanisms, such as anastasis and caspase-mediated proliferation, to survive after initiating apoptosis and other forms of regulated cell death.

Wild-type TP53 (p53) activity frequently enforces cell-cycle arrest, senescence, or quiescence programs that overlap with features of cellular dormancy, whereas loss or mutation of TP53 can alter dormant-cell survival, reactivation, and clonal outgrowth [15]. In their study, Antolino et al. [16] used liquid biopsies from patients affected by pancreatic ductal adenocarcinoma (PDAC) to sequence, using next-generation sequencing, the main genes involved in pancreatic carcinogenesis, namely KRAS, TP53, SMAD4, and CDKN2A, in an effort to pinpoint high-risk populations. In their patient population, TP53 polymorphism rs1042522 seemed to confer a 6- to 20-fold-increased odds ratio for PDAC compared to a reference population. Interestingly, rs1042522 is responsible for the susceptibility of Northwestern Chinese populations to gastric and esophageal cancer, in addition to other cancer types such as gliomas, non-Hodgkin lymphoma, and lung, bladder, prostate, colorectal, and breast cancer [17–20]. The authors concluded that the detection of TP53 polymorphisms may improve patient selection for early PDAC diagnosis with the application of therapeutic regimens at the initial stages of the disease in an effort to improve clinical outcomes.

In multiple myeloma (MM), the amount of clonal plasma cells remaining in the bone marrow after treatment is assessed to evaluate residual disease [21]. These surviving myeloma cells may enter a dormant state and, if reactivated, can cause relapse. Myeloma cells also evade immune control by impairing antigen-presenting cells, such as dendritic cells and macrophages, thereby blocking T-cell activation [22,23], and by reducing the presence of natural killer (NK) cells in the bone marrow [24]. From a clinical standpoint, physical functioning and quality of life (QoL) are important secondary endpoints because MM and its symptoms can worsen both aspects. These outcomes are interrelated: poorer physical function correlates with lower QoL in patients with plasma cell disorders [25]. Indeed, individuals with MM exhibit reduced physical function and QoL compared with healthy controls [26], and newly diagnosed patients fare worse than those who are two or more years post-diagnosis [25]. These findings suggest that tumor burden adversely affects everyday functioning in MM patients; however, it remains unclear whether characteristics of the bone marrow microenvironment contribute to this impact. In the study by Spiliopoulou et al. [27], the authors aimed to examine whether features of the bone marrow milieu are associated with physical function and QoL in patients who completed first-line therapy for MM. It was hypothesized that higher counts of bone marrow immune effectors with antitumor activity, such as T cells and NK cells, would be linked to better physical function and improved QoL. The authors report that the proportions of major cell types within the bone marrow microenvironment are not associated with physical performance in MM patients following first-line therapy. Objectively measured physical function instead correlates with other variables, notably lean body mass. Notably, the study authors observed elevated frequencies of $CD27^{+}$ NK/NKT cells, a finding that may reflect enhanced immune surveillance in bone marrow, and this increase was linked to improved quality of life in MM patients.

Cancer cells can escape the effects of conventional chemotherapeutic agents through differentiation, de-differentiation into a slow cycling cell population, and/or entering a senescence state, collectively referred to as cellular dormancy [28]. These clinical observations highlight the need for improved molecular strategies, combinations, and/or sequential therapies that target cancer cells without allowing growth arrest. In an experimental model of tumor dormancy for head and neck cancer, probucol, a strong antioxidant, exhibited

significant antitumor activity [29]. In their review article, Shukla et al. [30] evidenced that anti-inflammatory and antioxidant agents hold promise for treating gynecologic cancers by lowering oxidative stress, resolving chronic inflammation, and modulating key oncogenic pathways. The results of preclinical studies show that these compounds can suppress tumor growth, trigger apoptosis, andincrease sensitivity to standard therapies, while early clinical trials hint at improved immune responses and reduced treatment-related toxicities. The authors note that clinical application is still nascent and emphasize the need for further studies to refine drug formulations, dosing schedules, and combination regimens with established treatments. They also stress the importance of identifying predictive biomarkers to enable patient selection and personalized therapy. Ultimately, Shukla et al. argue that deepening our understanding of the molecular interplay between oxidative stress, inflammation, and gynecologic cancer biology is essential to translate these promising agents into effective, modern treatment strategies that enhance patient outcomes and QoL.

In the review by Boydell et al. [31], the authors synthesize current knowledge about the mechanistic pathways that enable tumors to enter and maintain a dormant state, with particular attention paid to the generation of antitumor immune responses and the synthesis of the local microenvironment that helps enforce dormancy. They argue that eradicating or controlling these quiescent cells could, in theory, secure durable remissions or even cures. However, to date, firm clinical proof for this strategy is lacking. The authors also highlight major technical hurdles: reliably detecting dormant cells, a core component of minimal residual disease, remains difficult. While disseminated tumor cells are arguably the most informative indicator, their assessment often depends on invasive sampling and limiting routine use. Ethical and logistical barriers further hamper trials: enrolling patients known to harbor residual disease into randomized studies (treatment versus observation) raises difficult moral questions. The authors note that preclinical systems have identified numerous cellular and niche-related drivers of dormancy, but these models poorly capture patient-specific host influences such as aging, chronic inflammation, lifestyle factors, and hormonal status. Given the many variables that modulate dormancy, Boydell et al. caution against expecting a single molecular target to solve the minimal residual disease problem. They conclude that incorporating dormancy-focused approaches into cancer care is promising but fraught with risks from treatment or procedure-related toxicity to the psychological burden on patients aware of lingering disease.

Cellular adaptations to environmental stress and the accompanying metabolic reprogramming are central to the establishment of cancer dormancy [32–34]. Yet the full spectrum of stress-response pathways and their contributions to malignant progression and dormancy remains incompletely defined. In their systematic review, Enwere et al. examined the effects of metabolism-targeted therapies, particularly interventions that modulate glucose and glutamine metabolism, on cancer treatment outcomes. They reviewed evidence that several natural compounds (notably curcumin, berberine, and high-dose vitamins C and D3) can interfere with glutamine uptake and attenuate the Warburg phenotype, and considered how these agents might be integrated with conventional therapies. The authors report that metabolic interventions, by targeting glycolysis and glutamine addiction, represent a promising complementary or alternative strategy for malignancies that are resistant to genetically targeted approaches, offering the potential for lower toxicity. They propose routine metabolic profiling to guide therapy selection and improve patient stratification and argue that personalization should incorporate metabolic and genetic risk factors (for example, G6PD deficiency when considering high-dose ascorbate and CYP polymorphisms relevant to berberine metabolism). Finally, Enwere et al. [35] call for standardized monitoring of hepatic, renal, and immune function to reduce adverse events and

recommend clinical evaluation of combined metabolic-targeted and conventional regimens to overcome tumor resistance and lower recurrence rates.

3. Conclusions

Integrating molecular insights, microenvironmental knowledge, and coordinated clinical efforts will enable the development of novel biomarkers that reliably stratify reactivation risk and the design of transformative therapies to prevent metastatic relapse. The articles included in this Special Issue offer new perspectives on understanding and targeting metastatic tumor dormancy and aim to catalyze researchers and clinicians to make dormancy a priority in oncology, with the potential to substantially improve patient outcomes and quality of life worldwide.

Author Contributions: Writing—Original Draft Preparation, C.N.B. and A.D.G.; Review and Editing, C.N.B. and A.D.G. All authors have read and agreed to the published version of the manuscript.

Funding: This article received no external funding.

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

References

1. Sosa, M.S.; Bragado, P.; Aguirre-Ghiso, J.A. Mechanisms of disseminated cancer cell dormancy: An awakening field. *Nat. Rev. Cancer* **2014**, *14*, 611–622. [CrossRef] [PubMed]
2. Manjili, M.H. Tumor Dormancy and Relapse: From a Natural Byproduct of Evolution to a Disease State. *Cancer Res.* **2017**, *77*, 2564–2569. [CrossRef] [PubMed]
3. Baxevanis, C.N.; Perez, S.A. Cancer Dormancy: A Regulatory Role for Endogenous Immunity in Establishing and Maintaining the Tumor Dormant State. *Vaccines* **2015**, *3*, 597–619. [CrossRef] [PubMed]
4. Aguirre-Ghiso, J.A.; Sosa, M.S. Emerging topics on disseminated cancer cell dormancy and the paradigm of metastasis. *Annu. Rev. Cancer Biol.* **2018**, *2*, 377–393. [CrossRef]
5. Risson, E.; Nobre, A.R.; Maguer-Satta, V.; Aguirre-Ghiso, J.A. The current paradigm and challenges ahead for the dormancy of disseminated tumor cells. *Nat. Cancer* **2020**, *1*, 672–680. [CrossRef]
6. Carneiro, B.A.; El-Deiry, W.S. Targeting apoptosis in cancer therapy. *Nat. Rev. Clin. Oncol.* **2020**, *17*, 395–417. [CrossRef]
7. Coppe, J.P.; Desprez, P.Y.; Krtolica, A.; Campisi, J. The senescence-associated secretory phenotype: The dark side of tumor suppression. *Annu. Rev. Pathol.* **2010**, *5*, 99–118. [CrossRef]
8. Huang, Q.; Li, F.; Liu, X.; Li, W.; Shi, W.; Liu, F.F.; O'Sullivan, B.; He, Z.; Peng, Y.; Tan, A.C.; et al. Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. *Nat. Med.* **2011**, *17*, 860–866. [CrossRef]
9. Ploumaki, I.; Triantafyllou, E.; Koumprentziotis, I.A.; Karampinos, K.; Drougkas, K.; Karavolias, I.; Trontzas, I.; Kotteas, E.A. Bcl-2 pathway inhibition in solid tumors: A review of clinical trials. *Clin. Transl. Oncol.* **2023**, *25*, 1554–1578. [CrossRef]
10. Savy, T.; Flanders, L.; Karpanasamy, T.; Sun, M.; Gerlinger, M. Cancer evolution: From Darwin to the extended Evolutionary Synthesis. *Trends Cancer* **2025**, *11*, 204–215. [CrossRef]
11. Maley, C.C.; Aktipis, A.; Graham, T.A.; Sottoriva, A.; Boddy, A.M.; Janiszewska, M.; Silva, A.S.; Gerlinger, M.; Yuan, Y.; Pienta, K.J.; et al. Classifying the evolutionary and ecological features of neoplasms. *Nat. Rev. Cancer* **2017**, *17*, 605–619. [CrossRef] [PubMed]
12. Das, J.; Overholtzer, M. Entosis in Health and Disease. *Adv. Exp. Med. Biol.* **2025**, *1481*, 293–303. [CrossRef] [PubMed]
13. Yumoto, K.; Eber, M.R.; Berry, J.E.; Taichman, R.S.; Shiozawa, Y. Molecular pathways: Niches in metastatic dormancy. *Clin. Cancer Res.* **2014**, *20*, 3384–3389. [CrossRef] [PubMed]
14. Mirzayans, R. When Therapy-Induced Cancer Cell Apoptosis Fuels Tumor Relapse. *Onco* **2024**, *4*, 37–45. [CrossRef]
15. Jackson, J.G.; Pant, V.; Li, Q.; Chang, L.L.; Quintas-Cardama, A.; Garza, D.; Tavana, O.; Yang, P.; Manshouri, T.; Li, Y.; et al. p53-mediated senescence impairs the apoptotic response to chemotherapy and clinical outcome in breast cancer. *Cancer Cell* **2012**, *21*, 793–806. [CrossRef]
16. Antolino, L.; Nucci, G.d.; Scarpino, S.; Bianco, G.; Lopez, G.; Aurello, P.; Petrucciani, N.; Santoro, R.; Nigri, G.; Agnes, S.; et al. Association of TP53 Arg72Pro (rs1042522) Polymorphism with Pancreatic Cancer Risk in a Patient Cohort. *Onco* **2025**, *5*, 44. [CrossRef]
17. Cao, J.; Chen, Z.; Tian, C.; Yu, J.; Zhang, H.; Yang, J.; Yang, W. A Shared Susceptibility Locus in the p53 Gene for both Gastric and Esophageal Cancers in a Northwestern Chinese Population. *Genet. Test. Mol. Biomark.* **2020**, *24*, 804–811. [CrossRef]

18. Eiholzer, R.A.; Mehta, S.; Kazantseva, M.; Drummond, C.J.; McKinney, C.; Young, K.; Slater, D.; Morten, B.C.; Avery-Kiejda, K.A.; Lasham, A.; et al. Intronic TP53 Polymorphisms Are Associated with Increased Delta133TP53 Transcript, Immune Infiltration and Cancer Risk. *Cancers* **2020**, *12*, 2472. [CrossRef]
19. Toscano-Guerra, E.; Maggio, V.; Garcia, J.; Semidey, M.E.; Celma, A.; Morote, J.; de Torres, I.; Giralt, M.; Ferrer-Costa, R.; Paciucci, R. Association of the rs1042522 SNP with prostate cancer risk: A study of cancer tissues, primary tumor cultures, and serum samples from a Spanish Caucasian population. *Front. Oncol.* **2024**, *14*, 1398411. [CrossRef]
20. Helal, E.A.; Hassan, N.M.; Kamel, M.M.; Amer, M.A.; Shafik, R.E. Contribution of TP53 and MDM4 Genetic Polymorphisms as a Risk Factor in Non-Hodgkin Lymphoma in Adult Egyptian Patients. *Clin. Med. Insights Oncol.* **2025**, *19*, 11795549251352047. [CrossRef]
21. Terpos, E.; Kostopoulos, I.V.; Kastritis, E.; Ntanasis-Stathopoulos, I.; Migkou, M.; Rousakis, P.; Argyriou, A.T.; Kanellias, N.; Fotiou, D.; Eleutherakis-Papaiakovou, E.; et al. Impact of Minimal Residual Disease Detection by Next-Generation Flow Cytometry in Multiple Myeloma Patients with Sustained Complete Remission after Frontline Therapy. *Hemasphere* **2019**, *3*, e300. [CrossRef] [PubMed]
22. Raitakari, M.; Brown, R.D.; Gibson, J.; Joshua, D.E. T cells in myeloma. *Hematol. Oncol.* **2003**, *21*, 33–42. [CrossRef] [PubMed]
23. Lopes, R.; Caetano, J.; Ferreira, B.; Barahona, F.; Carneiro, E.A.; Joao, C. The Immune Microenvironment in Multiple Myeloma: Friend or Foe? *Cancers* **2021**, *13*, 625. [CrossRef] [PubMed]
24. Ponzetta, A.; Benigni, G.; Antonangeli, F.; Sciume, G.; Sanseviero, E.; Zingoni, A.; Ricciardi, M.R.; Petrucci, M.T.; Santoni, A.; Bernardini, G. Multiple Myeloma Impairs Bone Marrow Localization of Effector Natural Killer Cells by Altering the Chemokine Microenvironment. *Cancer Res.* **2015**, *75*, 4766–4777. [CrossRef]
25. Jensen, C.E.; Vohra, S.N.; Nyrop, K.A.; Deal, A.M.; LeBlanc, M.R.; Grant, S.J.; Muss, H.B.; Lichtman, E.I.; Rubinstein, S.M.; Wood, W.A.; et al. Physical Function, Psychosocial Status, and Symptom Burden Among Adults with Plasma Cell Disorders and Associations with Quality of Life. *Oncologist* **2022**, *27*, 694–702. [CrossRef]
26. Gulbrandsen, N.; Hjermstad, M.J.; Wisloff, F.; Nordic Myeloma Study, G. Interpretation of quality of life scores in multiple myeloma by comparison with a reference population and assessment of the clinical importance of score differences. *Eur. J. Haematol.* **2004**, *72*, 172–180. [CrossRef]
27. Spiliopoulou, P.; Rousakis, P.; Panteli, C.; Eleutherakis-Papaiakovou, E.; Migkou, M.; Kanellias, N.; Ntanasis-Stathopoulos, I.; Malandrakis, P.; Theodorakakou, F.; Fotiou, D.; et al. The Role of the Bone Marrow Microenvironment in Physical Function and Quality of Life in Patients with Multiple Myeloma After First-Line Treatment with Novel Agents and Autologous Transplantation. *Onco* **2025**, *5*, 21. [CrossRef]
28. Yeh, A.C.; Ramaswamy, S. Mechanisms of Cancer Cell Dormancy—Another Hallmark of Cancer? *Cancer Res.* **2015**, *75*, 5014–5022. [CrossRef]
29. Nishimura, G.; Yanoma, S.; Satake, K.; Ikeda, Y.; Taguchi, T.; Nakamura, Y.; Hirose, F.; Tsukuda, M. An experimental model of tumor dormancy therapy for advanced head and neck carcinoma. *Jpn. J. Cancer Res.* **2000**, *91*, 1199–1203. [CrossRef]
30. Shukla, S.; Shukla, A.K.; Ray, N.; Upadhyay, A.M.; Fahad, F.I.; Dutta, S.D.; Nagappan, A.; Mongre, R.K. Targeting Pathways and Mechanisms in Gynecological Cancer with Antioxidant and Anti-Inflammatory Phytochemical Drugs. *Onco* **2025**, *5*, 24. [CrossRef]
31. Boydell, E.; Borgeaud, M.; Tsantoulis, P. Dormant Tumor Cells: Current Opportunities and Challenges in Clinical Practice. *Onco* **2025**, *5*, 3. [CrossRef]
32. Chen, X.; Iliopoulos, D.; Zhang, Q.; Tang, Q.; Greenblatt, M.B.; Hatziapostolou, M.; Lim, E.; Tam, W.L.; Ni, M.; Chen, Y.; et al. XBP1 promotes triple-negative breast cancer by controlling the HIF1alpha pathway. *Nature* **2014**, *508*, 103–107. [CrossRef]
33. Schewe, D.M.; Aguirre-Ghiso, J.A. ATF6alpha-Rheb-mTOR signaling promotes survival of dormant tumor cells in vivo. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 10519–10524. [CrossRef]
34. Pommier, A.; Anaparthy, N.; Memos, N.; Kelley, Z.L.; Gouronnec, A.; Yan, R.; Auffray, C.; Albrengues, J.; Egeblad, M.; Iacobuzio-Donahue, C.A.; et al. Unresolved endoplasmic reticulum stress engenders immune-resistant, latent pancreatic cancer metastases. *Science* **2018**, *360*, eaao4908. [CrossRef]
35. Enwere, M.; Irobi, E.; Chime, V.; Ezeogu, A.; Onu, A.; El Hussein, M.T.; Ogungbade, G.; Davies, E.; Omoniwa, O.; Omale, C.; et al. Metabolic Reprogramming as a Therapeutic Target in Cancer: A Qualitative Systematic Review (QualSR) of Natural Compounds Modulating Glucose and Glutamine Pathways. *Onco* **2025**, *5*, 43. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.