XPO1: From basic research to clinical treatment (Review)

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Abstract. Exportin 1 (XPO1) is a key nuclear export receptor that mediates the nuclear export of tumor suppressor proteins and growth-regulatory mRNAs from the nucleus to the cytoplasm. In several types of cancer, XPO1 is overexpressed or hyperactivated, leading to aberrant cytoplasmic sequestration of key tumor suppressors such as p53, p21, p73, FOXO and Rb. This mislocalization abrogates their nuclear transcriptional functions, disrupting cell cycle arrest, apoptosis and DNA repair, thereby promoting uncontrolled proliferation, survival and therapy resistance. Targeting XPO1 with selective inhibitors of nuclear export (SINE) has emerged as a promising anticancer strategy. The present review systematically examines the molecular mechanisms of XPO1-driven tumorigenesis and its rationale as a therapeutic target. The present review focuses on the clinical translation of SINE drugs, especially selinexor (KPT-330), in hematologic and solid tumors, critically assesses the limitations of monotherapy and explores the mechanistic basis for synergistic combination strategies. Ongoing clinical trials and future directions to optimize therapeutic efficacy are also highlighted. Collectively, the present review aims to provide a comprehensive foundation for advancing basic and clinical research on XPO1-targeted therapies.

Contents

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1. Introduction

The global incidence of cancer continues to rise annually (1), making it a major and growing public health challenge worldwide (2). Recent data indicate that in 2026, the United States is expected to have ~2.11 million new cases of cancer (~5,800 per day) and 626,000 cancer-related mortalities (~1,720 per day). The lifetime risk of developing cancer is similar between sexes, with 39.2% for men and 38.7% for women. Colorectal cancer is the third most common cancer in both men and women (3). Current standard cancer therapies include surgical resection, radiotherapy, chemotherapy and small-molecule targeted drug therapy. Among these, targeted therapy offers a precision approach by specifically modulating known oncogenic driver pathways at the cellular and molecular level across distinct tumor subtypes, thereby suppressing malignant cell proliferation while minimizing damage to healthy tissues. However, its clinical utility is constrained by the limited number of actionable driver alterations and the frequent emergence of acquired resistance during treatment (4-6). Therefore, there is an urgent need to identify novel therapeutic targets and systematically elucidate the molecular mechanisms underlying resistance to targeted therapies.

The nucleocytoplasmic compartmentalization of eukaryotic cells represents a fundamental structural hallmark that distinguishes them from prokaryotic cells. Macromolecules such as proteins and RNA must undergo selective and active transport through the nuclear pore complex (NPC) to enable precise nucleocytoplasmic communication (7). Among the key mediators of this process, exportin 1 (XPO1), also known as chromosome region maintenance 1 (CRM1), serves as the predominant nuclear export receptor. XPO1 specifically recognizes and binds cargo proteins containing leucine-rich nuclear export signals (NES), thereby facilitating their translocation from the nucleus to the cytoplasm (8). In numerous

cancer types, XPO1 is frequently overexpressed, leading to the aberrant nuclear export and cytoplasmic sequestration of key tumor suppressor proteins (TSPs), including p53, p21, FOXO and Rb, resulting in their functional inactivation. This prevents the execution of essential tumor-suppressive functions such as transcriptional regulation, cell cycle arrest and apoptosis within the nucleus, a phenomenon widely recognized as 'nuclear exclusion of tumor suppressor proteins (9,10). Consequently, pharmacological inhibition of XPO1 offers a mechanistically compelling strategy for cancer therapy by blocking the pathological export of TSPs, enabling their nuclear retention and functional restoration, and ultimately triggering cell cycle arrest and apoptosis in malignant cells. Although the early XPO1 inhibitor leptomycin B demonstrated potent target binding, its clinical development was halted due to severe systemic toxicity, poor pharmacokinetic stability and negligible oral bioavailability, which collectively precluded the establishment of a safe and effective therapeutic window (11). The emergence of next-generation selective inhibitors of nuclear export (SINE) compounds, particularly orally bioavailable agents such as Selinexor, has overcome these limitations. These agents exhibit improved tumor selectivity and manageable safety profiles, and have advanced into clinical trials for various hematologic malignancies and solid tumors, thereby markedly accelerating the clinical translation of XPO1-targeted cancer therapies (12).

In summary, XPO1 is frequently overexpressed across multiple types of cancer, driving tumorigenesis, progression, metastasis and treatment resistance by aberrantly exporting key TSPs. This establishes XPO1 as a key therapeutic target. The present review systematically summarizes recent advances in XPO1 biology in malignancies, detailing its dual regulation of tumor-suppressive pathways (for example, p53, FOXO or p21) and oncogenic signaling (for example, NF-κB or c-Myc). The present review also assesses its clinical relevance as a prognostic biomarker and therapeutic target. Focusing on SINEs, particularly the oral agent selinexor, the present review highlights clinical translation in hematologic malignancies (multiple myeloma (MM), diffuse large B-cell lymphoma (DLBCL)) and an expanding range of solid tumors. The present review critically examines the limitations of monotherapy, including modest efficacy and dose-limiting toxicities (fatigue, nausea, thrombocytopenia), and explore the mechanistic rationale and emerging evidence for synergistic combinations with chemotherapy, targeted agents or immunotherapy. By systematically evaluating completed and ongoing clinical trials, the present review identifies current challenges and outlines future optimization strategies, including next-generation SINEs, biomarker-driven precision dosing, individualized treatment regimens and investigation of acquired resistance mechanisms. The present review aims to provide a comprehensive framework of theoretical and translational insights to advance XPO1-targeted basic research and improve clinical application of XPO1 inhibition in oncology.

2. Literature selection methodology

To ensure a robust and comprehensive evaluation of the literature, a systematic search was performed across public databases including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/) and ClinicalTrials.gov (https://clinicaltrials.gov/). The literature search covered publications from 1997 through early 2026. Search terms utilized combinations of keywords and Medical Subject Headings (MeSH), including: 'XPO1', 'CRM1', 'Selinexor', 'KPT-330', 'SINE compounds', 'nuclear export inhibition' and 'acquired resistance'. Inclusion criteria comprised peer-reviewed original basic research articles, randomized controlled trials (RCTs), open-label phase I/II trials and molecular mechanistic studies published in English. Priority was allocated to 2024-2026 therapeutic readouts, structural updates and biomarker discoveries to maximize review timeliness.

3. The biological functions of XPO1 and tumorigenesis

XPO1 structure. XPO1 is a nuclear export receptor belonging to the importin-β superfamily of karyopherins and plays a central role in mediating the nuclear export of cargo proteins by recognizing their NES (13,14). Notably, XPO1 is the only known exportin responsible for transporting leucine-rich NES-containing proteins from the nucleus to the cytoplasm, a function that is critically dependent on its distinct structural architecture. XPO1 harbors a specialized binding pocket that specifically recognizes and engages NES motifs (7). These motifs are typically short, hydrophobic peptide sequences enriched in leucine residues and the precise amino acid composition and three-dimensional conformation of the NES-binding domain allow XPO1 to form complementary interactions with the hydrophobic side chains within the NES, akin to a lock-and-key mechanism, enabling selective binding to NES-bearing proteins or ribonucleoprotein (RNP) complexes (15,16). In addition, XPO1 contains a high-affinity binding site for Ran-GTP, a small GTPase that regulates nucleocytoplasmic transport (17). The association of Ran-GTP with XPO1 induces a conformational change that stabilizes the interaction between XPO1 and its cargo, facilitating the formation of the export-competent XPO1-cargo-Ran-GTP ternary complex and enabling its translocation through the NPC (18). Upon reaching the cytoplasm, hydrolysis of Ran-GTP to Ran-GDP triggers a structural rearrangement that promotes cargo release, thereby completing the export cycle (19). Furthermore, XPO1 possesses a distinct NPC-interacting domain that mediates transient interactions with phenylalanine-glycine (FG)-repeat nucleoporins located within the NPC. This interaction allows the export complex to dock at and traverse the nuclear pore, ensuring directional transport from the nucleus to the cytoplasm (18).

In summary, based on the aforementioned domains, XPO1 can mediate the nuclear export of RNA or proteins, thereby participating in the regulation of numerous biological processes.

The normal physiological function of XPO1. Eukaryotic cells establish functional compartmentalization between the nucleus and cytoplasm through the NPC, which also serves as the primary conduit for nucleocytoplasmic exchange of macromolecules and signaling molecules. Consequently, the NPC plays a key role in maintaining cellular homeostasis and

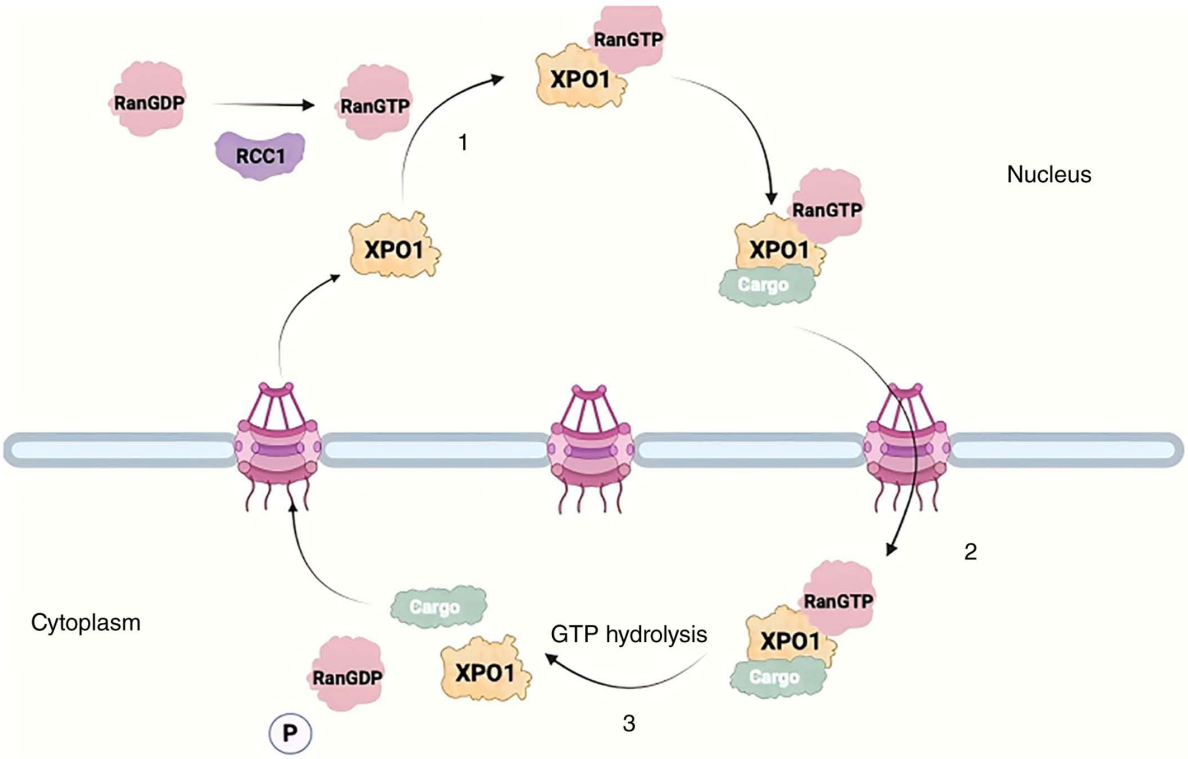

Figure 1. The RanGTP-mediated nuclear export macromolecular process. In the cytoplasm, RanGDP is converted to RanGTP by the guanine nucleotide exchange factor RCC1. XPO1 binds coordination-competent RanGTP and its leucine-rich NES cargo within the nucleus to form a stable trimeric export complex. This complex docks at and actively translocates through the nuclear pore complex via interactions with FG-repeat nucleoporins. Upon cytoplasmic entry, GTP hydrolysis is stimulated by RanGAP, triggering complex dissociation, cargo unloading and the subsequent nuclear reentry of XPO1 and RanGDP to drive subsequent export rounds. RanGTP, Ras-related nuclear protein bound to guanosine triphosphate; RanGDP, Ras-related nuclear protein bound to guanosine diphosphate; RCC1, Regulator of Chromosome Condensation 1; XPO1, Exportin 1, also known as CRM1; Chromosome Region Maintenance 1; NES, Nuclear Export Signal; FG-repeat nucleoporins, Phenylalanine-Glycine repeat nucleoporins; RanGAP, Ran GTPase-activating protein.

functions (8,15). The NPC is a large, evolutionarily conserved protein complex embedded within the nuclear envelope, exhibiting an octagonal symmetry and a characteristic three-dimensional architecture that resembles a 'basketball hoop' when viewed laterally (20). It is primarily composed of multiple copies of ~30 distinct nucleoporins (Nups), which are precisely organized into subcomplexes to form a central transport channel that facilitates selective macromolecular trafficking (21). This central channel permits passive diffusion of small molecules, such as ions and low-molecular-weight metabolites, while the translocation of larger macromolecules, including proteins and RNA species, requires active, signal-dependent transport mechanisms mediated by nuclear transport receptors (17).

The XPO1-mediated nuclear export process proceeds through a well-orchestrated sequence of molecular events. First, substrate recognition occurs: XPO1 specifically identifies cargo proteins containing NES (22). The NES is a short peptide motif enriched in hydrophobic amino acids, particularly leucine, and typically spans 10-30 residues (10). XPO1 binds tightly to the NES via its dedicated binding domain, initiating the export process. This interaction is highly selective, ensuring that only cargoes bearing functional NES motifs, such as specific proteins or RNP complexes, are recruited for nuclear export (23). Second, formation of the export complex takes place: Upon substrate binding, XPO1 associates with Ran-GTP, a small GTPase that acts as a key regulatory cofactor, to assemble a stable trimeric export complex (XPO1-cargo-Ran-GTP) (24). The binding of Ran-GTP induces a conformational change in XPO1 that enhances its affinity for the cargo and stabilizes the complex, thereby rendering it translocation-competent (25). Third, docking and translocation through the NPC occur: The assembled trimeric complex is directed to the NPC, where XPO1 interacts with phenylalanine-glycine (FG)-repeat nucleoporins via its NPC-binding domain, facilitating docking at the nuclear side of the pore. The NPC, a large transmembrane channel embedded in the nuclear envelope, serves as the sole gateway for nucleocytoplasmic transport. Through transient interactions with FG-Nups, the complex undergoes facilitated translocation across the NPC toward the cytoplasm (22). Finally, cargo release and recycling are achieved in a GTP hydrolysis-dependent manner. Upon reaching the cytoplasm, Ran-GTP is hydrolyzed to Ran-GDP by RanGAP and its cofactors, triggering a conformational rearrangement in XPO1 that reduces its affinity for both the cargo and Ran-GDP. This leads to the dissociation of the cargo into the cytoplasm. Subsequently, XPO1 and Ran-GDP are recycled back to the nucleus for subsequent rounds of export, completing the transport cycle (18,26) (Fig. 1).

The XPO1-mediated nuclear export process plays a pivotal role in cell cycle regulation. For example, cyclin-dependent kinase inhibitors p21 and p27 are actively exported from the nucleus by XPO1, thereby modulating their nuclear

accumulation and subsequently regulating CDK activity and cell cycle progression (27,28). Similarly, transcription factors of the FOXO family are constitutively shuttled out of the nucleus by XPO1 under basal conditions, limiting their access to target genes involved in apoptosis and antioxidant defense; upon cellular stress, inhibition of XPO1 leads to nuclear retention of FOXO proteins, enabling them to activate transcriptional programs essential for stress resistance and cell fate control (29,30). The tumor suppressor p53 is also subject to XPO1-dependent regulation, following completion of DNA damage repair, XPO1 mediates the nuclear export of p53 to attenuate its transcriptional activity and prevent prolonged cell cycle arrest or aberrant apoptosis (31,32). Through this dynamic spatial control of key regulatory proteins, XPO1 fine-tunes key cellular processes including proliferation, differentiation and homeostasis. Beyond these functions, XPO1 contributes notably to the regulation of cellular stress responses and inflammatory signaling. In the NF-κB pathway, degradation of IκBα releases NF-κB for nuclear translocation and activation of pro-inflammatory genes, whereas XPO1 counteracts this activation by exporting NF-κB, often as a complex with newly synthesized IκBα, back to the cytoplasm, thus providing negative feedback to limit the duration and intensity of NF-κB signaling and prevent chronic inflammation (33,34). Furthermore, under oxidative stress or heat shock, XPO1 regulates the nucleocytoplasmic trafficking of stress-responsive transcription factors such as HSF1, ensuring timely induction of cytoprotective gene expression programs (35). In addition, XPO1 facilitates the nuclear export of specific mRNAs, particularly those encoding growth regulators and oncoproteins, thereby extending its regulatory influence to post-transcriptional control of gene expression (36,37).

In summary, XPO1 is not only a central mediator of nucleocytoplasmic transport but also a key regulatory hub that integrates intracellular and extracellular signals with essential cellular processes. Maintenance of its normal physiological function is vital for maintaining cellular homeostasis, ensuring proper signal transduction and enabling spatiotemporal regulation of key molecular events. Dysregulation of XPO1 function can result in the mislocalization of key regulatory proteins, thereby disrupting cell fate decisions and contributing to tumorigenesis and cancer progression. Therefore, a comprehensive understanding of the molecular mechanisms underlying XPO1 activity not only advances fundamental knowledge in cell biology but also provides a solid theoretical foundation for developing targeted therapies against its pathological dysregulation.

Abnormalities of XPO1 in tumors. In various hematological malignancies (such as MM (12), DLBCL (38) or acute myeloid leukemia (39)) and solid tumors (including ovarian cancer (40), gastric cancer (41), pancreatic cancer (42) or glioblastoma (43)), the expression level of XPO1 is markedly higher than that in the corresponding normal tissues. Moreover, multiple clinical studies have confirmed that its high expression is associated with poor prognosis, accelerated disease progression, and chemotherapy resistance in patients (44). A large number of immunohistochemical, RT-qPCR and gene expression profiling data show that the protein and mRNA levels of XPO1 are abnormally upregulated in tumor tissues, suggesting that it is not only a functional driver in the process of tumorigenesis but may also serve as a potential prognostic biomarker (45). Studies have found that XPO1 promotes tumor occurrence and development at multiple levels by mediating the abnormal nuclear export of key TSPs and regulatory factors, thereby disrupting their normal subcellular localization and functional activity (10,26,46,47).

p53 pathway impairment (clinically validated). In the p53 signaling pathway, XPO1 actively exports both p53 and its upstream DNA damage sensor kinase ATM from the nucleus, resulting in their aberrant cytoplasmic accumulation and functional inactivation (47,48). Excessive nuclear export of these proteins severely impairs their transcriptional regulatory functions, compromising genomic surveillance, increasing mutational burden and thereby facilitating malignant transformation. This mechanism is particularly important and clinically validated in hematologic malignancies and specific solid tumors harboring wild-type p53, providing a mechanistic explanation for the observed loss-of-function phenotype despite an intact p53 gene (32,49).

Cell cycle dysregulation (preclinical and sample-based validation). XPO1 drives cell cycle dysregulation by mediating the nuclear exclusion of key tumor suppressors. For example, the CDK inhibitors p21 and p27, key negative regulators of the G_1/S transition, exert their inhibitory effects on cyclin-CDK complexes when localized in the nucleus (9); similarly, the retinoblastoma (Rb) protein suppresses S-phase gene expression by sequestering E2F transcription factors (48). Under conditions of XPO1 overexpression, these proteins are constitutively exported from the nucleus, leading to unchecked cell cycle progression and uncontrolled tumor cell proliferation. Moreover, p73 is subject to XPO1-mediated nuclear export and inactivation, further undermining the integrity of the tumor suppressor network (49).

Apoptosis evasion pathways (preclinical models). XPO1 suppresses apoptosis by exporting pro-apoptotic factors. The FOXO family of transcription factors (for example, FOXO1 and FOXO3a) induces expression of pro-apoptotic genes under stress conditions; however, elevated XPO1 activity promotes rapid nuclear export and subsequent degradation of FOXO proteins, abolishing their apoptotic function (50,51). Similarly, Bim, a pivotal pro-apoptotic member of the Bcl-2 family, exerts its mitochondrial-stabilizing and caspase-activating effects primarily when retained in the nucleus, but its efficacy is diminished by XPO1-dependent nuclear export (52,53). Notably, survivin can also be exported by XPO1 in specific splice variants, modulating its stability and distribution, thereby indirectly tipping the balance toward cell survival (54).

Oncogenic signaling amplification (cell and animal models). In inflammatory and proliferative signaling pathways, XPO1 enhances NF-κB activation by exporting IκBα, the endogenous inhibitor of NF-κB, thereby releasing NF-κB from cytoplasmic sequestration and enabling its nuclear translocation and transcriptional activation of pro-inflammatory, anti-apoptotic and pro-migratory genes (50,51,55). Concurrently, XPO1 exports

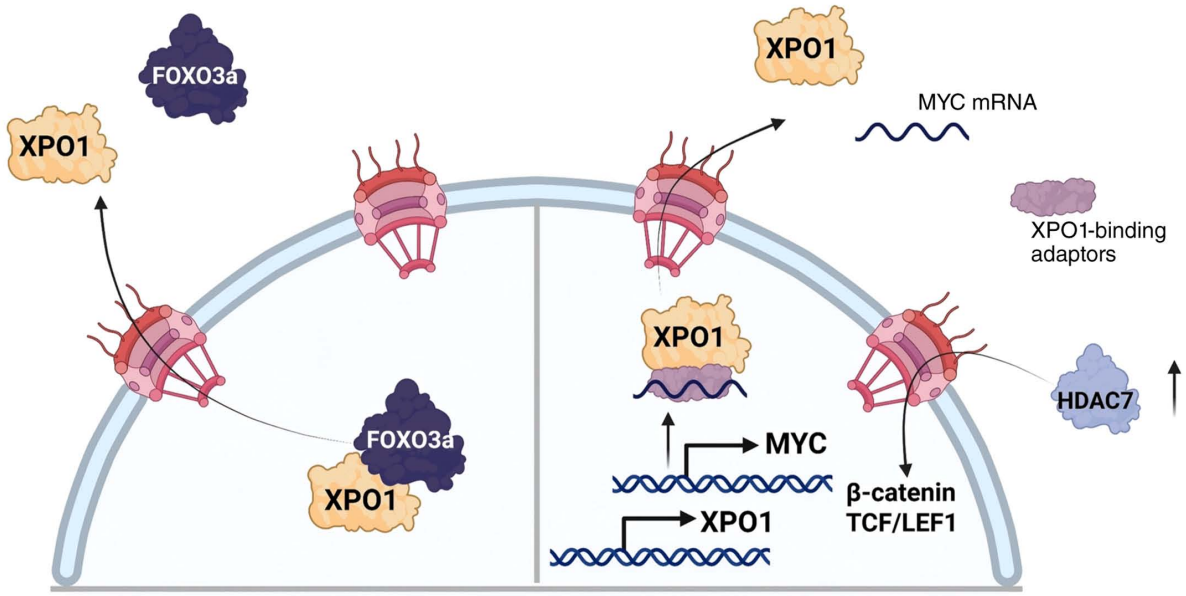

Figure 2. Sub-regulatory networks and downstream pathological targets altered by XPO1 upregulation. Schematic mapping of the structural interaction cascades of overexpressed XPO1 with essential homeostasis molecules. The schematic displays the selective nuclear exclusion and cytoplasmic inactivation of proteins (including FOXO3a, p53, p21 and Rb), alongside the coordinated nuclear-to-cytoplasmic shuttling of oncogenic MYC mRNA transcripts, β-catenin, TCF/LEF1 and structural histones such as HDAC7, demonstrating how the hijacking of this transport system drives multi-pathway oncogenesis. FOXO3a, Forkhead box O3a; p53, Tumor protein p53; p21, Cyclin-dependent kinase inhibitor 1A; Rb, Retinoblastoma protein; MYC, MYC proto-oncogene; TCF, T-cell factor; LEF1, Lymphoid enhancer-binding factor 1; HDAC7, Histone deacetylase 7.

eIF4E from the nucleus, facilitating its cytoplasmic assembly into translation initiation complexes and selectively enhancing the translation of oncogenic mRNAs, including c-Myc, cyclin D1 and VEGF (56-58). In lymphomas, XPO1 overexpression mediates the nuclear export of STAT6, leading to increased levels of phosphorylated STAT6? and accelerated tumor cell proliferation (59). Furthermore, while nuclear accumulation of MYC drives malignant proliferation, XPO1 contributes to MYC oncogenicity by regulating its nucleocytoplasmic shuttling to maintain MYC protein stability (56) (Fig. 2).

In summary, XPO1 drives tumorigenesis through a coordinated and multifaceted mechanism by systematically altering the subcellular localization of key regulatory proteins, thereby disrupting key cellular processes such as the DNA damage response, cell cycle control, apoptosis and signal transduction. This 'multi-target hijacking' strategy enables XPO1 to simultaneously impair multiple tumor-suppressive pathways, positioning it as a highly compelling therapeutic target in oncology. Targeting XPO1 therefore offers a dual advantage: it not only restores the functional integrity of diverse tumor suppressor networks but also counters chemotherapy resistance and potentiates the effectiveness of current treatment modalities. As such, XPO1 inhibition represents a strategy with substantial potential for both advancing fundamental cancer biology and enabling meaningful clinical translation.

4. Clinical translational research on SINE

SINE are a class of small-molecule compounds that specifically target the function of XPO1. Substantial progress has been achieved in the clinical translation of SINE compounds in oncology (55). These agents irreversibly inhibit XPO1-mediated nuclear export by covalently binding to the cysteine 528 within the cargo-binding pocket of XPO1, thereby blocking its ability to recognize and transport cargo proteins (60,61) (Fig. 3). This inhibition results in the nuclear retention and re-accumulation of key TSPs, including p53, p21, FOXO and Rb, restoring their transcriptional activity and triggering downstream anti-tumor effects such as cell cycle arrest, apoptosis and enhanced chemosensitivity in cancer cells (62). Among the SINE family, selinexor (KPT-330) is the most extensively characterized compound and the most clinically advanced compound (63). Selinexor exhibits favorable oral bioavailability, favorable pharmacokinetic stability and effective blood-brain barrier (BBB) penetration, demonstrating potent anti-tumor activity across diverse hematologic malignancies and solid tumor models. Currently, selinexor has received approval from the U.S. FDA for the treatment of relapsed or refractory MM (RRMM) and DLBCL. Moreover, numerous global phase I/II clinical trials are underway to evaluate its efficacy and safety as monotherapy or in combination with chemotherapy, targeted agents and immune checkpoint inhibitors in indications such as acute myeloid leukemia (AML), castration-resistant prostate cancer and advanced ovarian cancer (64-66). These studies not only validate XPO1 as a therapeutically viable anticancer target but also provide key insights for the further refinement and precision application of SINE-based therapies (Table I).

Clinical research in hematological malignancies. The SINE selinexor, a representative compound in its class, has demonstrated notable antitumor activity across various hematological malignancies, with its clinical translation achieving notable breakthroughs (67). Particularly in the treatment of refractory or relapsed diseases, selinexor offers a novel therapeutic option for patients who have failed conventional therapies by

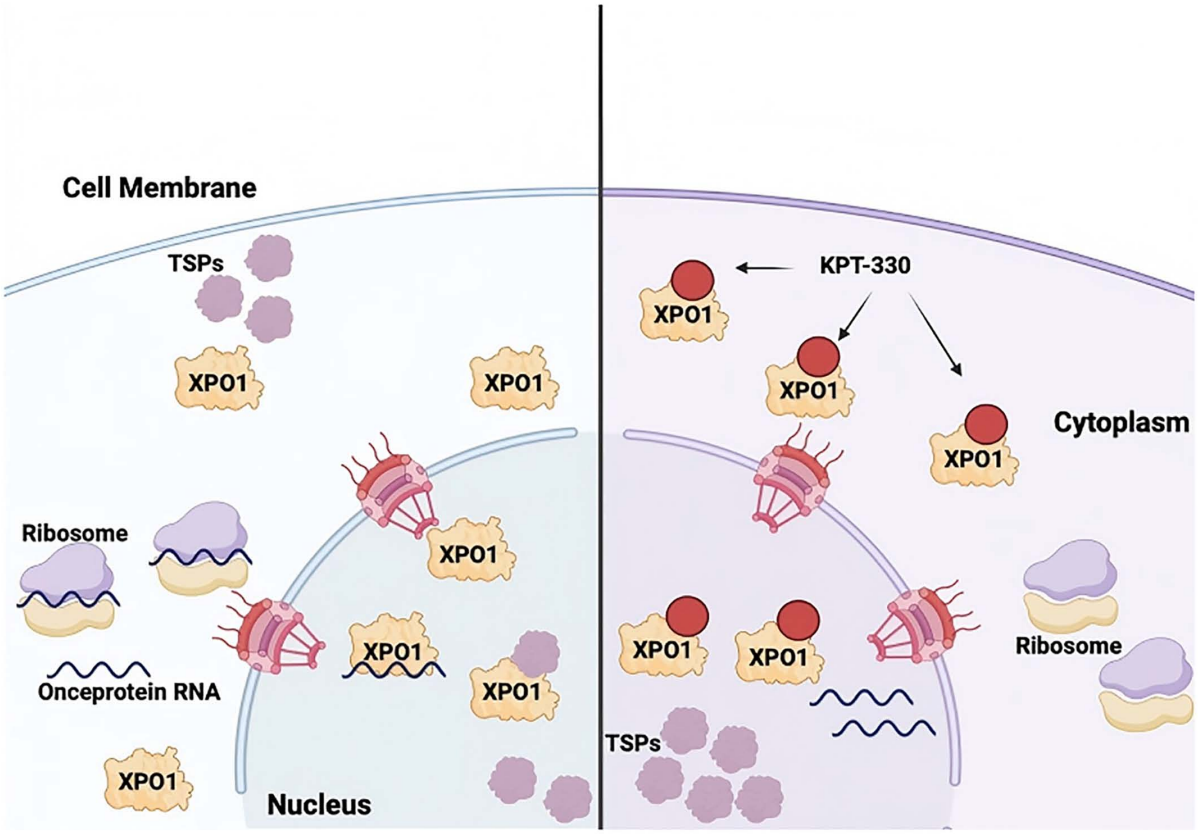

Figure 3. Subcellular distribution of XPO1 cargo and the impact of KPT-330 blockade. (Left) Under physiological states, baseline XPO1 mediates the normal export of functional regulatory substrates (proteins, ribosomal subunits and mRNAs encoding oncoproteins) out of the nucleus. (Right) Following the introduction of the SINE small-molecule compound KPT-330 (selinexor), the compound forms an irreversible covalent bond with the structural Cys528 residue inside the cargo pocket. This blocks cargo binding, alters XPO1 compartmental orientation, stops macromolecular transport and forces the nuclear retention and functional reactivation of key TSPs. TSPs, tumor suppressor proteins; KPT-330, Selinexor, a selective inhibitor of nuclear export; SINE, Selective inhibitor of nuclear export; Cys528, Cysteine residue at position 528 of the XPO1 protein.

restoring the nuclear localization and transcriptional function of key TSPs.

FDA-approved indications and randomized phase III evidence. The BOSTON Trial (Phase III RCT): Further validation for MM came from the BOSTON trial, a randomized, open-label, phase III study comparing the triplet regimen of once-weekly selinexor, bortezomib and dexamethasone (SVd) vs. the standard doublet Vd (bortezomib plus dexamethasone) in patients with RRMM. The SVd arm demonstrated a statistically notable improvement in median progression-free survival (PFS), with particularly pronounced benefits observed in patients who had received only 1-3 prior lines of therapy. Moreover, the SVd regimen yielded higher overall response rates and complete response rates, indicating synergistic antitumor activity. As a result, the SVd regimen was incorporated into international treatment guidelines as a standard-of-care option for eligible patients with RRMM (64,68,69). A subsequent review further validated these findings by systematically demonstrating that selinexor-containing regimens maintain consistent efficacy across multiple difficult-to-treat MM subpopulations, including triple-class refractory disease, renal impairment, high-risk cytogenetics and prior anti-CD38 therapy. An ongoing phase Ib/II trial is evaluating the quadruplet of selinexor with carfilzomib, isatuximab and dexamethasone in RRMM, while another phase II trial is assessing SVd-like induction specifically in newly diagnosed MM with extramedullary disease. Notably, selinexor is now being explored as maintenance therapy following CAR-T cell treatment, reflecting its expanding role across the MM treatment continuum. The SENTRY Trial (XPORT-MF-034; Phase III RCT): In myelofibrosis, a disease setting previously unexplored for XPO1 inhibition, the randomized, double-blind, placebo-controlled SENTRY trial evaluated selinexor (60 mg once weekly) in combination with ruxolitinib vs. placebo plus ruxolitinib in JAK inhibitor-naïve patients. Results released in March 2026 demonstrated that the trial met its first co-primary endpoint of spleen volume reduction ≥35% (SVR35) at week 24: 50 vs. 28% (one-sided P<0.0001), with rapid, deep and durable spleen responses and a promising overall survival signal. Although the second co-primary endpoint of symptom improvement was not reached, this landmark study positions selinexor as a potential first-in-class targeted therapy in myeloproliferative neoplasms (70).

Regulatory milestones from single-arm phase II trials. The STORM Trial (Phase IIb, Single-Arm): In the field of MM, the STORM study enrolled patients with penta-refractory disease, defined as resistance to at least five major drug classes: Proteasome inhibitors, immunomodulatory agents, anti-CD38 monoclonal antibodies, alkylating agents and glucocorticoids. Despite this extensive prior treatment and refractoriness,

Table I. Therapeutic application of XPO1 inhibitors in clinical tumor patients.

Tumor type	Trial phase	Patient number (n)	Dosage regimen	Primary efficacy outcomes	Common & and significant adverse events (≥grade 3)	Key conclusions/ remarks	(Refs.)
Advanced solid tumors	Phase I	189	3-85 mg/m², in 21/28-day cycles	In 157 evaluable patients: CR, 1 (0.6%); PR, 6 (4%); SD (≥4 months), 17%	Hematologic, thrombocytopenia (16%); non-hematologic, fatigue (15%)	Demonstrated preliminary anti-tumor activity. Established the recommended Phase II Dose (RP2D) as 35 mg/m² (~60 mg), twice weekly; toxicity requires management.	(92,110)
Non-Hodgkin's Lymphoma	Phase I	79	3-80 mg/m², in 3/4-week cycles	In 70 evaluable patients: CR, 4; PR, 18; ORR, 31.4%	Thrombocytopenia (47%); Neutropenia (32%); Anemia (27%)	Responses observed across multiple NHL subtypes. RP2D was 35 mg/m² (60 mg). Provides initial evidence for monotherapy in NHL.	(96)
Multiple myeloma	Phase I	81 (MM)	3-60 mg/m², 1-3 times per week	In 57 monotherapy patients: PR, 4%; MR, 18%; SD, 32%; some patients had treatment duration <2 years	Grade ≥3 AEs not emphasized in text	Even patients achieving only MR or SD could achieve long-term disease control, suggesting clinical benefit.	(98)
Acute myeloid leukemia	Phase I	95	4, 8, 10 mg/m², in 21/28-day cycles	In 81 evaluable patients: ORR, 14%; 31% of patients had ≥50% reduction in marrow blasts	Fatigue (14%) (non-hematologic)	RP2D determined as 60 mg (~35 mg/m²) twice weekly. Non-hematologic toxicities were manageable.	(111)
Metastatic castration-resistant prostate cancer	Phase II	14	Not specified (twice weekly)	Limited efficacy; only 2 patients had >50% PSA decline	Severe anorexia, nausea, fatigue	Limited clinical activity and poor tolerability hindered further development in this population.	(112)
Advanced/ metastatic gynecologic cancer (ovarian, endometrial, cervical)	Phase II (SIENDO)	114	35 or 50 mg/m² twice weekly; or 50 mg/m² once weekly (QW)	Primary safety assessment; 50 mg/m² QW regimen had fewer high-grade AEs	AEs were reversible and manageable with supportive care	The once-weekly 50 mg/m² regimen demonstrated an improved safety profile.	(113)
HMA-refractory MDS/ oligoblastic AML	Phase II	23	60 mg, twice weekly, 2 weeks on/ 1 week off	Response rate, 24-26%	Tolerable	First trial using a lower fixed dose (60 mg), showing good activity and tolerability, facilitating longer-term treatment.	(114)

Table I. Continued.

Tumor type	Trial phase	Patient number (n)	Dosage regimen	Primary efficacy outcomes	Common & and significant adverse events (≥grade 3)	Key conclusions/ remarks	(Refs.)
Recurrent glioblastoma	Phase II	76	50 mg/m², or 60 mg (twice weekly), or 80 mg (once weekly, QW)	Primary endpoint: 6-month Progression-Free Survival rate (PFS6)	Fatigue (61%), nausea (59%), anorexia (43%), thrombocytopenia (43%)	Toxicity was manageable at 80 mg once weekly, adjustable via dose reduction.	(115)
Advanced/ recurrent endometrial carcinoma	Phase III (SIENDO)	174	Not specified (once weekly oral)	PFS showed statistically significant improvement (HR, 0.71; P=0.049)	Not specified in detail	KPT-330 showed significant clinical promise in post-chemotherapy advanced/recurrent endometrial cancer.	(116)
Advanced dedifferentiated liposarcoma	Phase II	56	Not specified	No significant PFS improvement	Not specified in detail	KPT-330 monotherapy did not show significant efficacy in this solid tumor.	(10)

AE, Adverse event; AML, Acute myeloid leukemia; CR, Complete response; HMA, Hypomethylating agent; HR, Hazard ratio; MDS, Myelodysplastic syndrome; MR, Minimal response; NHL, Non-Hodgkin's Lymphoma; ORR, Overall response rate; PFS, Progression-free survival; PR, Partial response; PSA, Prostate-specific antigen; RP2D, Recommended Phase II dose; SD, Stable disease; SIENDO, Selinexor in Endometrial Cancer Clinical Trial.

the combination of selinexor and low-dose dexamethasone achieved an overall response rate (ORR) of ~26%, with some patients attaining a very good partial response or better. Based on these findings, the FDA granted accelerated approval in 2019 for selinexor in combination with dexamethasone for the treatment of RRMM (64,71). The SADAL Trial (Phase II, Single-Arm): In DLBCL, the SADAL study evaluated selinexor monotherapy in patients with relapsed/refractory disease. The trial reported an ORR of 28% in the overall population, with a complete response rate of 12%; notably, patients with the germinal center B-cell-like subtype showed a trend toward improved outcomes. Given this clinical benefit, the FDA approved selinexor in 2020 for the treatment of relapsed/refractory DLBCL in patients ineligible for intensive chemotherapy or CAR-T cell therapy (71-75).

Early exploratory trials AML and T-cell lymphomas. In AML, early-phase I/II studies have demonstrated that selinexor combined with azacitidine or low-dose cytarabine can induce complete remissions in elderly or unfit patients, with particular promise in those harboring TP53 mutations or complex karyotypes. In T-cell lymphomas, including peripheral T-cell lymphoma and mycosis fungoides, small studies have documented stable disease or partial responses (76-83).

In conclusion, selinexor has demonstrated substantial clinical value across a range of hematological malignancies, particularly in patients with highly refractory disease who have limited therapeutic options. Its ability to induce responses in such heavily pretreated populations underscores its distinctive mechanism of action and ongoing therapeutic relevance. As understanding of the drug's pharmacodynamics and predictive biomarkers continues to evolve, there is strong potential for refining patient selection and developing individualized treatment strategies that maximize clinical benefit.

Clinical exploration and efficacy limits in solid tumors. Although research on SINE has advanced more rapidly in hematological malignancies, their clinical exploration in solid tumors has increasingly demonstrated potential antitumor activity and therapeutic value. Selinexor, the first-in-class SINE, is undergoing extensive evaluation in multiple refractory solid tumor types, leveraging its favorable oral bioavailability and robust tissue penetration properties. Although clinical evaluation in solid tumors is ongoing, these indications face more prominent barriers. The clinical efficacy of XPO1 inhibitors in solid tumors is currently less established than in hematological malignancies, frequently characterized by modest PFS gains, limited OS extensions and heightened toxicity profiles (84).

Randomized controlled trials in specialized soft tissue tumors. The SEAL Trial (Phase III RCT): In advanced dedifferentiated liposarcoma (DDLS), the SEAL study evaluated the efficacy and safety of selinexor monotherapy in patients who had progressed after multiple prior therapies. Results demonstrated that Selinexor notably prolonged median PFS compared with placebo. However, overall OS did not show a statistically significant difference, a notable clinical limitation given the relentless course characteristic of DDLS.

Mechanistically, DDLS is frequently driven by amplification of the 12q13-15 region, resulting in overexpression of MDM2 and CDK4; inhibition of XPO1 prevents the nuclear export and subsequent degradation of TSPs, including p53 and Rb, thereby partially restoring their activity (54,85).

Phase II validation and maintenance cohorts, endometrial carcinoma maintenance. In gynecologic malignancies, the phase III SIENDO trial evaluated oral selinexor as maintenance therapy after first-line chemotherapy for advanced or recurrent endometrial cancer. The primary analysis showed a statistically significant improvement in median PFS (HR, 0.71; P=0.049), suggesting a potential role for XPO1 inhibitors as a maintenance approach.

Glioblastoma multiforme (GBM). Preclinical evidence confirms that selinexor effectively crosses the BBB. In phase II clinical settings, selinexor monotherapy has been shown to induce cell cycle arrest and promote nuclear retention of key TSPs. Early-phase clinical trials have confirmed the feasibility of combining selinexor with temozolomide, with observations of disease stabilization in a small subset of patients, though dose-limiting toxicities remain a primary obstacle (86-90).

Early preclinical or phase I combinations: Ovarian, lung and pancreatic types of cancer. In ovarian cancer, early phase I studies indicate that combining selinexor with paclitaxel or PARP inhibitors can elicit responses in platinum-resistant populations. In non-small cell lung cancer, preliminary phase I data suggest that selinexor enhances the efficacy of pembrolizumab by upregulating tumor cell surface expression of MHC class I molecules. In pancreatic ductal adenocarcinoma, the combination of selinexor with gemcitabine or nab-paclitaxel has demonstrated disease control rates in small phase I/II cohorts, though further large-scale validation is required to determine efficacy (91-94).

In summary, although the development of SINE in solid tumors remains at an intermediate level, these agents have already demonstrated measurable biological activity and promising clinical benefit in specific tumor subtypes. Future efforts should focus on identifying robust predictive biomarkers, refining combination regimens and improving toxicity management to advance their translational potential in precision oncology for solid tumors.

Clinical toxicity and patient compliance management. The practical deployment of selinexor is considerably restricted by prominent constitutional and hematological toxicities. Rather than being easily managed, these adverse events frequently necessitate immediate treatment interruption, substantial dose reduction or permanent discontinuation, thereby compromising treatment continuity and diminish clinical efficacy.

Hematological adverse events. Thrombocytopenia is the primary dose-limiting hematological toxicity, occurring in up to 43-47% of patients in aggressive schedules (95,96). It requires rigorous weekly monitoring, proactive dose modifications and the implementation of supportive care such as platelet transfusions or thrombopoietin receptor agonists. Neutropenia and anemia are also frequently reported (96,97).

Gastrointestinal and constitutional events. Nausea, vomiting, severe anorexia and fatigue represent profound challenges to patient compliance. Nausea affects >59% of patients, while fatigue affects >61% in some cohorts. To sustain patient adherence, modern dosing protocols have shifted away from initial high-dose, twice-weekly regimens toward once-weekly lower fixed-dose regimens (for example, 60 or 80 mg once weekly) combined with aggressive, multi-agent prophylactic antiemetic regimens (including NK1 receptor antagonists and 5-HT3 antagonists) (72,73,98).

5. Next-Generation SINE compounds and synergy strategies

Next-generation SINE compounds. As the therapeutic potential of XPO1 inhibitors continues to evolve, next-generation SINE compounds are under active development to address the pharmacological limitations of selinexor. Eltanexor (KPT-8602) achieves reduced central nervous system toxicity compared with selinexor primarily through structural modifications that lower BBB penetration and shorten target residence time. While eltanexor maintains covalent binding to the Cys528 residue of XPO1, it exhibits modified binding kinetics that result in a shorter duration of target engagement in neuronal cells, thereby sparing the prolonged suppression of nucleocytoplasmic transport key for normal CNS function. Pharmacokinetically, eltanexor was engineered to reduce affinity for the efflux transporter P-glycoprotein (P-gp) at the BBB; this alteration, together with decreased passive permeability, yields notably lower brain-to-plasma ratios than selinexor, limiting drug accumulation in the CNS compartment while preserving effective antitumor concentrations in peripheral tumors and hematopoietic tissues. These molecular and pharmacokinetic features collectively attenuate the neurotoxic effects, such as confusion, ataxia and cognitive disturbance, observed with more CNS-penetrant SINEs and translate clinically into a substantially reduced incidence of severe nausea, vomiting and fatigue. Preclinical and phase I clinical data confirm that eltanexor exerts robust antitumor activity in AML and MM models, offering an improved therapeutic index and greater tolerability for long-term administration. Verdinexor (KPT-335): Initially developed and approved for veterinary oncology in canine lymphoma, verdinexor features high oral bioavailability and extensive peripheral tissue distribution. It is now under evaluation in human preclinical models, demonstrating unique promise in prostate cancer, HIV-associated malignancies and virus-associated malignancies (99-102).

Mechanism-guided combination therapies. Combination therapy represents the central strategic direction for the future development of selective nuclear export inhibitors. Because XPO1 regulates multiple intersecting signaling networks, its inhibition can enhance the sensitivity of conventional cytotoxic agents, targeted drugs and immunotherapies through distinct synergistic mechanisms.

Chemotherapy sensitization (high clinical maturity) SINE-mediated XPO1 blockade impairs DNA repair pathways, including homologous recombination (HR) and non-homologous end joining (NHEJ), rendering tumor cells more vulnerable to chemotherapy-induced DNA

double-strand breaks. Clinically, selinexor combined with cytarabine or anthracyclines has been shown to improve complete remission rates in patients with AML, while its combination with gemcitabine has demonstrated enhanced disease control in pancreatic cancer. Furthermore, a phase I study of selinexor in combination with high-dose cytarabine and mitoxantrone (HiDAC/Mito) achieved an overall response rate of 70% in newly diagnosed or relapsed/refractory AML, confirming that SINE compounds successfully potentiate the efficacy of DNA-damaging agents. In aggressive lymphomas, XPO1-mediated mRNA export of genome maintenance regulators actively drives chemotherapy resistance, making the combination with standard cytotoxic regimens mechanistically sound (74,75).

Targeted therapy synergy (moderate clinical maturity), proteasome inhibitors. SINE compounds counteract oncogenic survival signals by blocking the nuclear export of IκBα, leading to nuclear retention of the inhibitor, deactivation of the NF-κB pathway and synergistic induction of apoptosis when paired with bortezomib or carfilzomib. BCL-2 Inhibitors: One of the most promising targeted combinations is the pairing of SINEs with the BCL-2 inhibitor venetoclax in AML. Venetoclax induces mitochondrial apoptosis, but resistance often emerges via MCL-1 upregulation. SINE compounds counteract this resistance by blocking the nuclear export of MCL-1 mRNA via eIF4E-dependent translational regulation, thereby reducing MCL-1 protein levels and restoring sensitivity to venetoclax. The 2026 phase Ib data on Selinexor-venetoclax in relapsed/refractory AML further confirmed the safety and clinical activity of this combination, while the eltanexor-venetoclax trial (NCT06399640) was initiated to extend this strategy to venetoclax-resistant AML populations (76).

PARP Inhibitors: Preclinical models across TNBC, SCLC and glioblastoma demonstrate that combining selinexor with olaparib notably increases anti-tumor activity by simultaneously blocking DNA damage repair and impairing compensatory lysosomal autophagy (55,82,83).

Immunotherapy and dual barrier blockade (preclinical/conceptual maturity) immune checkpoint blockade. SINEs induce nuclear retention of PD-L1, potentially altering its membrane expression dynamics and sensitizing tumors to PD-1/PD-L1 blockade. In preclinical models, combining selinexor with anti-PD-1 antibodies results in marked tumor growth suppression, though large-scale clinical validation is still pending (77). Dual blockade of nuclear pores: This is a highly innovative approach that simultaneously inhibits nuclear export (through XPO1) and nuclear import (through import proteins α/β). Since inhibiting XPO1 alone may lead to compensatory increases in nuclear import, it is hypothesized that dual targeting can trigger more severe nuclear-cytoplasmic transport disorders, trapping regulatory proteins in the wrong cellular compartments and inducing tumor cell death. This strategy is currently entirely in the preclinical stage (102,103). However, since nuclear-cytoplasmic transport is key for all eukaryotic cells, simultaneously inhibiting XPO1 and import proteins α/β is expected to have an impact on healthy tissues, particularly those with high proliferation rates and active protein transport, such as hematopoietic precursor cells, gastrointestinal epithelial cells and neural progenitor cells. The expected toxic challenges include exacerbated bone marrow suppression (such as thrombocytopenia and neutropenia), cumulative disruption of transcription factor localization in normal cells and potential neurotoxicity resulting from the disruption of nuclear transport in non-dividing neurons. Nevertheless, The present review also notes the differential transport dependence between tumor cells and normal cells, as well as emerging strategies such as tumor-targeted drug delivery and intermittent dosing regimens, which may provide therapeutic windows to mitigate these risks (78,79).

6. Other SINE compounds and combination strategies

As the therapeutic potential of SINE in oncology continues to emerge, next-generation SINE compounds, such as eltanexor (KPT-8602) and verdinexor (KPT-335), are under active development alongside Selinexor, which has advanced into late-stage clinical trials (80,81). These novel agents are designed to preserve potent XPO1 inhibition while improving pharmacokinetic profiles, minimizing toxicity and broadening the spectrum of clinical indications. Eltanexor, a structurally optimized derivative of Selinexor, maintains covalent binding to the Cys528 residue of XPO1 but exhibits a shorter half-life and reduced brain penetration, thereby markedly attenuating central nervous system-related adverse events, including nausea, anorexia and fatigue (80). Preclinical studies demonstrate that Eltanexor exerts robust antitumor activity in models of AML, MM and solid tumors, with an improved tolerability profile compared with Selinexor (82). Ongoing phase I/II clinical trials are evaluating its safety and preliminary efficacy as monotherapy or in combination regimens for relapsed or refractory hematologic malignancies, showing encouraging translational potential. By contrast, Verdinexor was initially developed for veterinary use in canine lymphoma and is now being translated into human oncology research. It features high oral bioavailability and extensive tissue distribution, demonstrating unique therapeutic promise in prostate cancer, HIV-associated malignancies and virus-associated malignancies (83).

Combination therapy is currently recognized as the central strategic direction for the future development of SINEs. Given that XPO1 regulates multiple key signaling pathways, its inhibition not only restores the nuclear functions of key TSPs but also disrupts DNA damage repair mechanisms and modulates the tumor immune microenvironment, thereby conferring broad potential for synergistic antitumor effects. Preclinical and clinical evidence indicates that SINE compounds can enhance the sensitivity of conventional cytotoxic agents through multiple mechanisms (Table II). For example, XPO1 inhibition promotes nuclear accumulation of pro-apoptotic factors such as p53, FOXO and p73, leading to reactivation of apoptotic pathways; concurrently, it suppresses sustained NF-κB activation, attenuating downstream anti-apoptotic and inflammatory responses. Furthermore, SINE-mediated XPO1 blockade impairs DNA repair pathways, including HR and NHEJ, rendering tumor cells more vulnerable to chemotherapy-induced DNA double-strand breaks. Clinically, selinexor in combination with cytarabine or anthracyclines has been shown to improve complete remission rates in patients

Table II. The combination treatment regimens of Selinexor and anti-tumor drugs that have emerged in clinical tumor treatment.

A, Combination with chemotherapy

Combination drug category	Specific combination drugs	Cancer type	Key findings/mechanism of action	Research phase	Key efficacy outcomes/ conclusions	(Refs.)
Paclitaxel-based	Gemcitabine + nab-Paclitaxel	Pancreatic ductal adenocarcinoma	Synergistically inhibits tumor growth; impacts tumor and stromal signaling; relocates TSP to the nucleus.	Phase Ib clinical trial	Disease control rate reached 80%. Well-tolerated in combination with GemPac, no DLTs observed.	(104,117)
	Paclitaxel (weekly)	Recurrent platinum-resistant ovarian cancer	Preclinical models showed anti-tumor activity.	Phase Ib clinical trial	RR, 17%; CBR, 58%; RP2D, Selinexor 60 mg (twice weekly) + Paclitaxel 80 mg/m^2.	(118)
Anthracyclines	Doxorubicin	Anaplastic thyroid carcinoma	Synergistically inhibits ATC cell proliferation.	Preclinical	Showed promising anti-tumor activity, providing a new theoretical basis for improving ATC patient outcomes.	(119)
	Daunorubicin + Cytarabine ('7+3')	AML	Selinexor and daunorubicin showed notable synergy in AML.	Phase I clinical trial	In newly diagnosed elderly/ unfit AML, ORR 53%, median OS 10.3 months. Selinexor 80 mg was safe with '7+3'.	(120)
Cytarabine	High-Dose Cytarabine + Mitoxantrone (HiDAC/Mito)	AML (newly diagnosed or R/R)	Synergy between Selinexor and DNA-damaging agents in leukemia cells.	Phase I clinical trial	ORR 70%, induction mortality 5%. RP2D, Selinexor 80 mg twice weekly.	(75,121)
	Fludarabine + Cytarabine (FLAG)	Pediatric R/R leukemia	Exploring Selinexor safety in pediatric patients.	Phase I clinical trial	Tolerable in pediatric patients. MTD for Selinexor was 55 mg/m^2.	(122)
Eribulin	Eribulin	Leiomyosarcoma, advanced triple-negative breast cancer	Synergistically enhances IκB-α nuclear localization, reduces NF-κB translocation; potent activity *in vivo* and *in vitro*.	Phase Ib Clinical trial	In TNBC/sarcoma: ORR, 10%; CBR, 71%; RP2D: Selinexor 80 mg weekly + Eribulin 1 mg/m^2.	(123-125)
Other chemotherapy	Azacitidine	AML	Synergistically induces AML cell apoptosis; downregulates XPO1, eIF4E and c-MYC.	Preclinical	Showed synergistic anti-leukemic activity.	(56)
	Cisplatin or Irinotecan	Small Cell Lung Cancer (SCLC)	Combination notably inhibited tumor growth in SCLC PDX models.	Preclinical	Provides a new therapeutic opportunity for SCLC.	(126)

Table II. Continued.

A, Combination with chemotherapy

Combination drug category	Specific combination drugs	Cancer type	Key findings/mechanism of action	Research phase	Key efficacy outcomes / conclusions	(Refs.)
	R-CHOP regimen	NHL	XPO1 overexpression is associated with poor prognosis in NHL; Selinexor is active as a single agent in DLBCL.	Phase I clinical trial	Combined with R-CHOP showed durable efficacy and acceptable long-term safety.	(127,128)

B, Combination with targeted therapy

Combination drug category	Specific combination drugs	Cancer type	Key findings/mechanism of action	Research phase	Key efficacy outcomes/ conclusions	(Refs.)
Proteasome inhibitors	Carfilzomib + Dexamethasone (SKd)	RRMM	Inactivates NF-κB pathway via IκBα nuclear retention; induces Bcl-2 reduction and Akt inactivation.	Phase I clinical trial	Safe and tolerable, showed notable efficacy. RP2D: Selinexor 60 mg + Carfilzomib 20/27 mg/m^2 + Dex 20 mg.	(129-131)
	Carfilzomib	Sarcoma	Stabilizes and enhances IκB nuclear localization, inhibiting NF-κB and survivin.	Preclinical	Increased sarcoma cell sensitivity to Selinexor.	(126)
Bcl-2 inhibitors	Venetoclax	GBM, AML, DHL	Selinexor downregulates Mcl-1 and counteracts Mcl-1 upregulation from Bcl-2 inhibition; enhances DNA damage in AML.	Preclinical	Shows synergistic anti-tumor effects in GBM, AML and DHL; a potential strategy.	(53,86,105)
PARP inhibitors	Olaparib	TNBC, SCLC, GBM	Synergistic proliferation inhibition in TNBC; restores FOXO3a activity in SCLC; inhibits DNA damage repair and blocks autophagy in GBM.	Preclinical	Considerably increased anti-tumor activity compared with monotherapy across multiple tumor types.	(132-134)
BTK inhibitors	Ibrutinib	MCL, CLL, PCNSL	Overcomes Ibrutinib resistance by inducing IκB nuclear retention inhibiting NF-κB; modulates macrophage polarization to enhance anti-tumor immunity.	Preclinical	Shows synergy in various B-cell lymphomas and can overcome Ibrutinib resistance.	(135-139)

Table II. Continued.

B, Combination with targeted therapy

Combination drug category	Specific combination drugs	Cancer type	Key findings/mechanism of action	Research phase	Key efficacy outcomes/ conclusions	(Refs.)
mTOR inhibitors	GSK2126458 (PI3K/mTORi)	TNBC	Showed promising anti-tumor activity in TNBC PDX models without acute toxicity.	Preclinical	Demonstrates strong anti-tumor activity.	(140)
	Everolimus	NHL	Enhances the activity of the mTOR inhibitor in NHL cell lines.	Preclinical	Potential application for Everolimus-resistant patients with NHL.	(141)

C, Other targeted

Combination drug category	Specific combination drugs	Cancer type	Key findings/mechanism of action	Research phase	Key efficacy outcomes/ conclusions	(Refs.)
FLT3 inhibitors	Midostaurin/Gilteritinib	AML (FLT3-ITD)	Synergistic anti-tumor effect, superior to single agents.	Preclinical	Shows synergistic anti-leukemic activity	(142)
AURKA inhibitor	Alisertib	NB	Combination markedly increased tumor cell death.	Preclinical	Notably enhanced anti-tumor effect *in vitro* and *in vivo* models.	(143)
CDK4/6 inhibitor	Palbociclib	HCC	Selinexor promotes RB1 nuclear localization, synergistically inducing senescence.	Preclinical	Synergistically induces senescence.	(44)

D, Other combinations

Combination drug category	Specific combination drugs	Cancer type	Key findings/mechanism of action	Research phase	Key efficacy outcomes/ conclusions	(Refs.)
Other (epigenetic/ hormonal)	TAM	ERα(+) Breast Cancer (TAM-resistant)	Affects Akt-related metabolic pathways, shuts down autophagy, overcomes TAM resistance.	Preclinical	Can overcome TAM resistance in recurrent ERα(+) breast cancer.	(144)
	Decitabine	AML	Decitabine priming enhances the anti-leukemic activity of lower-dose Selinexor.	Preclinical	May improve patient tolerance without compromising efficacy.	(141)

Table II. Continued.

Combination drug category	Specific combination drugs	Cancer type	Key findings/mechanism of action	Research phase	Key efficacy outcomes/ conclusions	(Refs.)
D, Other combinations						
	Dexamethasone	Triple-class RMM	Combination induces myeloma cell apoptosis.	Phase II clinical trial	26% of patients achieved ≥ Partial Response, 39% achieved ≥ Minimal Response.	(64)
	FLAG-Ida Chemotherapy					(145)

ATC, Anaplastic thyroid carcinoma; CBR, Clinical benefit rate; CLL, Chronic lymphocytic leukemia; DHL, Double-hit lymphoma; DLT, Dose-limiting Toxicity; MTD, Maximum tolerated dose; ORR, Overall response rate; OS, Overall survival; PCNSL, Primary central nervous system lymphoma; PDX, Patient-derived xenograft; R/R, Relapsed or refractory; RP2D, Recommended phase II dose; SCLC, Small cell lung cancer; TNBC, Triple-negative breast cancer; TSP, Tumor suppressor protei.

with AML (74,75), while its combination with gemcitabine has demonstrated enhanced disease control in pancreatic cancer (104). In the context of targeted therapy, one of the most promising combinations is the pairing of SINEs with the BCL-2 inhibitor venetoclax in AML (55,82,83). Venetoclax induces mitochondrial-dependent apoptosis by selectively inhibiting BCL-2; however, resistance, often driven by MCL-1 upregulation or p53 pathway dysfunction, is a major limitation (105). SINE compounds counteract this resistance by blocking the nuclear export of MCL-1 mRNA via eIF4E-dependent translational regulation, thereby reducing MCL-1 protein levels, while simultaneously restoring functional activity of p53 and p73. Early-phase clinical data demonstrate favorable response rates with this combination in elderly and relapsed/refractory patients with AML, with manageable toxicity, positioning it as a leading investigational strategy (86). Beyond chemotherapy and targeted agents, SINEs exhibit notable potential in immunotherapy by reshaping the tumor immune microenvironment. Although NF-κB signaling is typically associated with pro-survival and inflammatory functions, controlled activation through XPO1 inhibition can trigger type I interferon responses, upregulate MHC class I molecules and tumor-associated antigens and promote dendritic cell maturation and T-cell recognition. Tumor cells treated with selinexor show increased susceptibility to CD8+ T cell-mediated clearance. Additionally, SINEs induce nuclear retention of PD-L1, potentially altering its membrane expression dynamics and sensitizing tumors to PD-1/PD-L1 blockade (77). In preclinical models, the combination of selinexor and anti-PD-1 antibodies results in marked tumor growth suppression and prolonged survival. Multiple ongoing phase I/II trials are actively evaluating the efficacy of SINE-immunotherapy combinations in non-small cell lung cancer, melanoma and microsatellite instability-high (MSI-H) solid tumors (77). A more innovative and forward-looking approach is the concept of 'nuclear pore double blockade', which involves dual inhibition of nuclear export (via XPO1) and nuclear import (via importin α/β). Nuclear-cytoplasmic shuttling is a tightly balanced process and monoinhibition of XPO1 may trigger compensatory increases in nuclear import. Dual targeting is therefore hypothesized to induce more profound disruption of nucleocytoplasmic trafficking, trapping key regulatory proteins in the wrong cellular compartment and exacerbating proteotoxic and transcriptional stress, ultimately driving tumor cell death (78,79). Although still in the preclinical stage, this strategy has demonstrated superior antitumor efficacy compared with single-pathway inhibition across multiple drug-resistant models, highlighting its potential as a novel paradigm in precision oncology.

In summary, the development of next-generation SINE compounds is advancing toward enhanced selectivity, improved safety profiles and expanded therapeutic indications. Leveraging their ability to modulate multiple signaling pathways, SINEs exhibit substantial synergistic potential when combined with diverse treatment modalities, including chemotherapy sensitization, targeted therapy synergy, immune activation and even dual targeting of the nuclear transport system. Future research must further define optimal combination regimens, robust predictive biomarkers and long-term safety to facilitate the transition of SINE-based

therapies from 'single-targeting' approaches to a new era of 'system-integrated' cancer treatment.

7. Structured framework of acquired resistance mechanisms

To facilitate the rational design of subsequent treatment strategies and circumvent therapeutic failure, the established and hypothetical mechanisms underlying resistance to XPO1 inhibitors are organized into a structured framework.

Target-specific point mutations. The most robustly documented mechanism of acquired resistance involves specific point mutations within the cargo-binding pocket of XPO1. Prolonged drug exposure drives the selection of malignant clones harboring a cysteine-to-serine mutation at position 528 (C528S). Because SINE compounds rely on forming a covalent bond with the sulfur atom of the Cys528 side chain, this substitution eliminates covalent drug binding while preserving endogenous nuclear export activity, rendering these inhibitors ineffective (87).

Upregulation of efflux transporters. Resistant tumor phenotypes frequently display marked transcriptional upregulation of ATP-binding cassette (ABC) transporters, most notably P-gp (encoded by ABCB1/MDR1). Upregulated P-gp accelerates the active efflux of small-molecule SINEs across the plasma membrane, reducing intracellular drug concentrations below the threshold required to achieve effective target occupancy (88,89).

Compensatory karyopherin expression shifts. When XPO1-mediated transport is chronically suppressed, tumor cells can undergo adaptive evolution by upregulating alternative, non-canonical nuclear export receptors, such as Exportin-5 (XPO5) and Exportin-7 (XPO7). These alternative transporters take over the nucleocytoplasmic shuttling of vital growth-regulatory mRNAs and tumor suppressors, bypassing XPO1 blockade and restoring the baseline malignant phenotype (90,91).

8. Discussion and future perspectives

Positioning XPO1 within the evolving biomarker landscape. The absence of validated predictive biomarkers presents a notable obstacle to precise clinical deployment. High XPO1 expression does not necessarily associate with sensitivity to XPO1 inhibition; instead, response is dictated by tumor suppressor status, nuclear export dependency, mutational background and complex RNA regulatory networks (92,93).

Research on tumor prognosis and therapeutic response biomarkers has moved from single-protein expression toward non-coding RNAs, multi-omics features and integrated regulatory networks. This trend is particularly evident in gastrointestinal and colorectal cancer, where numerous clinical evaluations have established that distinct long non-coding RNA and microRNA profiles serve as superior predictive and prognostic indicators compared with traditional immunohistochemistry. Integrating XPO1 biomarker development into this multi-omic landscape offers notable translational opportunities: Synthetic lethality profiling, high-throughput sequencing enables the systematic discovery of genetic alterations, such as TP53 mutations, KRAS aberrations or distinct transcriptomic expression signatures, associated with sensitivity to XPO1 inhibition. For instance, tumors with p53 dysfunction may exhibit heightened dependence on XPO1-mediated survival pathways, rendering them vulnerable to selective inhibition through a synthetic lethal interaction. Dynamic PET Probes: The development of novel positron emission tomography (PET) probes capable of targeting the XPO1 active site represents n achievable near-term clinical realistic goal. Such probes could enable non-invasive, real-time imaging of nuclear export activity and track the subcellular redistribution of TSPs, offering a dynamic approach to patient stratification and early assessment of therapeutic response (94,106-108).

Advanced translational strategies: XPO1-Directed PROTACs. To overcome point mutations (for example, C528S) that render traditional small-molecule inhibitors ineffective, proteolysis-targeting chimera (PROTAC) technology has emerged as a transformative frontier (52,99). Unlike conventional SINEs that merely block protein function, XPO1-directed PROTACs function as bifunctional molecules that recruit specific E3 ubiquitin ligases, such as cereblon (CRBN) or von Hippel-Lindau (VHL), to tag XPO1 for polyubiquitination and subsequent proteasomal degradation. Preclinical proof-of-concept studies demonstrate that PROTAC platforms provide distinct advantages over traditional competitive inhibition (100). Because PROTACs rely on transient, event-driven binding rather than permanent covalent attachment to the Cys528 residue, they retain full degradative capacity against C528S-mutant clones, successfully preventing acquired resistance (101). Furthermore, PROTACs drive the physical destruction of the XPO1 receptor rather than temporary occupancy, inducing more prolonged suppression of nucleocytoplasmic transport and triggering apoptosis at lower concentration thresholds (44). Dual inhibition of XPO1 and cell-cycle regulators has also revealed an acquired vulnerability exploitable by CRBN-based PROTACs in preclinical models (102). Moreover, by optimizing the linker length and selecting tissue-selective E3 ligases, next-generation chimeras can be engineered to minimize degradation within normal hematopoietic precursor cells, potentially mitigating severe clinical toxicities such as thrombocytopenia (103). Importantly, the off-target profiles of PROTACs and covalent inhibitors such as selinexor arise from fundamentally distinct mechanisms: selinexor's dose-limiting toxicities result from systemic, on-target inhibition of XPO1's physiological export functions across all tissues, whereas PROTACs introduce a unique off-target landscape driven by the recruited E3 ligase, CRBN-based degraders may inadvertently target IKZF1/3 zinc-finger transcription factors, while VHL-recruiting chimeras could perturb the hypoxia-inducible factor pathway (109). However, these risks can be managed by engineering E3 ligase ligands with attenuated neosubstrate activity, fine-tuning linker chemistry to restrict degradation to specific conformational states of XPO1 or exploiting E3 ligases with restricted tissue expression. Therefore, PROTACs effectively decouple therapeutic efficacy from the on-target toxicities inherent to

pan-XPO1 covalent inhibition, offering a path toward a more favorable safety profile (44,101).

9. Conclusion

In conclusion, XPO1 represents a novel and promising anti-cancer target that has achieved a pivotal 'from zero to one' breakthrough in clinical translation and is now entering a key phase of expansion, from 'one to many' toward broader therapeutic applications in solid tumors. The future advancement of this field will depend on the deep integration of basic research, translational medicine and clinical practice. At the fundamental level, further elucidation of the comprehensive regulatory mechanisms of the nuclear export machinery and identification of its tumor-specific vulnerabilities are essential. Translational efforts must prioritize the clinical validation of robust predictive biomarkers and the mechanistic dissection of resistance pathways, while clinical development must utilize sophisticated trial designs to optimize the balance between efficacy and safety. Despite existing challenges, ongoing research and innovation will undoubtedly position XPO1-targeted nuclear export inhibition as an increasingly integral component of future precision oncology.

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Authors' contributions

YP and YT involved in the conception and design of the study. YP, YT, CY, JZ, XZ, XH and JZ wrote the first draft of the review, while XZ, XH and JZ collected the information needed for the review, including references and images. YT and YP revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript. YT and YP have seen and can confirm the authenticity of the raw data.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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