Review Article

Stem Cell INVESTIGATION

The past, present, and future of CRM1/XPO1 inhibitors

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Abstract: Therapies targeted at inhibiting nucleo-cytoplasmic transport have found broad applications in the field of oncology. Chromosome region maintenance 1 (CRM1), better known as exportin 1 (XPO1), is the protein transporter responsible for the nucleo-cytoplasmic shuttling of most of the tumor suppressor proteins (TSP) and growth regulatory factors. XPO1 is also upregulated in many malignancies and associated with a poor prognosis. Its inhibition has been a target of therapy, and hence, the selective inhibitors of nuclear transport (SINE) compounds were developed as a novel class of anti-cancer agents. The most well-known SINE agent is selinexor (KPT-330) and has been widely tested in phase I and II clinical trials in both solid tumors and hematologic malignancies. This review discusses how dysregulation of XPO1 promotes tumorigenesis, the historical considerations in the development of SINE compounds, and their role in current clinical therapies.

Keywords: Selinexor; chromosome region maintenance 1/exportin 1 inhibitors (XPO1/CRM1 inhibitors)

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Introduction

The regulation of protein transport across the nuclear membrane is essential for maintaining cellular homeostasis but this process is altered in tumor cells (1). While smaller molecules can passively diffuse through the nuclear pore complex (NPC), larger cargo molecules (>40 kDa) require active transport via transport receptors (2-5). These receptor proteins belong to the karyopherin beta family and are further classified into importins (for nuclear import), exportins (for nuclear export), and transportins (for both import and export) (4). Exportins are better studied as potential targets in tumorigenesis (6-8). The most important and best studied exportin is CRM1, which forms a ring-like structure consisting of 21 HEAT repeats. Cargo proteins displaying a leucine-rich nuclear export signal (LR-NES) bind to the hydrophobic groove formed by HEAT repeats 11 and 12 on the outer convex surface of CRM1 (9,10). A small GTPase Ran loaded with GTP then binds cooperatively with CRM1 to power the translocation of the CRM1-cargo-RanGTP complex through the NPC. Once the complex reaches the cytoplasm, it encounters RanBP1 to facilitate cargo release, as well as RanGAP1 to catalyze the hydrolysis of RanGTP to RanGDP (4,10). This process is tightly regulated by the GTP exchange factor, regulator of chromosome condensation 1 (RCC1), which is an exclusive nuclear protein responsible for reforming RanGTP from RanGDP. Its cytoplasmic counterpart is RanGAP1, and both ensure tight control of the import-export process through maintaining the Ran GDP:GTP gradient (11). It is through this nucleus-to-cytoplasm translocation of regulatory proteins that allows the cell to direct its proliferation or apoptosis pathways (6).

CRM1: first forgotten, then rediscovered

CRM1 is present in all eukaryotic cells and was initially identified as a chromosomal mutation in the yeast *schizosaccharomyces pombe* (12). Also known as exportin 1 or XPO1, it is responsible for the transport of over 200 proteins, which include many tumor suppressor proteins (TSP) and oncoproteins (11,13). In addition, CRM1 plays an essential role in mitosis through (I) binding and targeting key mitotic proteins to specific areas of the mitotic spindle; and (II) stabilizing the microtubule kinetochore to promote proper chromosomal segregation (14). Inhibition of RCC1, which regulates CRM1, by actinomycin D resulted in severe spindle assembly defects and mitotic catastrophe (15). Among the list of CRM1-mediated proteins are p53, FOXOs, p27, nucleophosmin, BCR-ABL, p21, PI3K/AKT, Wnt/β-catenin, NF-kB, APC, and Rb, all of which are significant targets in oncogenesis (6-8,11). Dysregulation of this transport process has been implicated in cancer, in addition to wound healing, inflammation, and viral infections (5,11). CRM1 overexpression has been demonstrated in both solid tumors and hematologic malignancies, and this overexpression is associated with a poorer prognosis and drug resistance (6,8). The exact mechanism by which this occurs remains unclear but is thought to involve altered transport mechanisms in favor of cytoplasmic localization and the modification of nuclear proteins to reveal their LR-NES enabling them to bind CRM1 (1,16).

Abnormal CRM1 upregulation can have several cancer-promoting consequences (6). Upregulation of CRM1 would allow more growth regulatory proteins, such as c-myc or BCR-ABL, to be transported into the cytoplasm and activate downstream signaling leading to sustained cell proliferation. Similarly, TSPs, such as Rb, p53, p21, or p27, are functionally inactivated upon export, hence removing the check on inappropriate cell growth. Similar disruptions would occur in the processes of apoptosis, DNA damage repair, chromosomal stabilization, and angiogenesis, just to name a few examples (6). Hence, inhibition of CRM1 activity became an attractive therapeutic target.

The first CRM1 inhibitor to be discovered was leptomycin B (LMB), which is naturally made by the bacteria Streptomyces (17,18). LMB was initially used as an anti-fungal agent, and its anti-cancer properties were discovered later (17,19). However, the clinical trials involving LMB were discontinued early due to profound cytotoxicity thought to be derived from permanent CRM1 inhibition (12,20). Several semi-synthetic CRM1 inhibitors were developed and studied in the pre-clinical setting, but unfortunately, none were ever entered into clinical trials (8). The next generation of compounds to be developed was collectively known as selective inhibitors of nuclear transport (SINE) compounds and include KPT-185, KPT-249, KPT-251, KPT-276, KPT-330, and KPT-335 (6). Similar to their predecessors, these molecules form covalent bonds to a cysteine residue (Cys528) on CRM1 (21). However, they improve upon the first-generation compounds by engaging in a slowly reversible covalent bonding, which improves upon the toxicity profile (22). The SINEs also cause a transient degradation of CRM1 that is reversible upon discontinuation of the SINE compound (6).

Somatic mutations in the CRM1 gene frequently occur in cancer cells, and they were initially identified in patients with CLL (23). Nearly 90% of the mutations involve an E571K amino acid change that resides near the NES-binding cleft. While this resulted in an increase in affinity for NES sequences bearing a more negatively charged C-terminal end, studies demonstrated that this mutational change did not impact the activity of CRM1 on nuclear transport or the efficacy of SINE compounds (24,25). However, if either a homozygous or heterozygous mutation involving the Cys528 residue was present, this conferred resistance to SINE compounds (26).

SINEs in the pre-clinical and clinical setting

Pre-clinical studies involving SINEs have demonstrated notable inhibition of tumor cell growth and promotion of cell apoptosis across a broad range of solid and hematologic malignancies, primarily through mediating the transport of key oncogenic proteins (see *Table 1*).

Selinexor or KPT-330 is the most well-known SINE and is currently undergoing study in about 60 clinical trials, involving lymphoma (i.e., Non-Hodgkin's lymphoma, diffuse large B-cell lymphoma), sarcomas, lung cancer, gliomas, breast cancer, leukemia (ALL, AML, MDS), multiple myeloma (MM), gastric cancer, pancreatic cancer, esophageal cancer, prostate cancer, melanoma, colorectal cancer, thymic cancer, and gynecologic cancers (see *Table 2*) (44).

Lung cancer

Selinexor offers an attractive therapeutic strategy in non-small cell lung cancer (NSCLC) through demonstrating

Table 1 Effect of CRM1/XPO1 inhibition on molecular targets of cancer

Target (nuclear accumulation)	Effect of CRM1/XPO1 inhibition	Cancer cell type
MDM2	Nuclear p53 retention and activation	AML (27)
NPM1	Restoration of nuclear NPM1	AML (27)
CEBPA	Nuclear retention and activation induces blast differentiation	AML (28,29)
FLT3	FLT3 reduction	AML (28)
KIT	KIT reduction	AML (28)
NF-κB	IκB nuclear retention and activation	CLL (30), NHL (31), MM (32)
Survivin	Promotion of apoptosis, inhibition of STAT3 binding	Breast cancer (33), NHL (31), various (1)
BCR-ABL	Reactivation of protein phosphatase 2A tumor suppressor and inhibition of BCR-ABL1	CML, ALL (34)
AKT pathway (AKT, PTEN, PI3K)	Downregulation of cell proliferation	AML (11), NSCLC (35)
p53	Restoration of nuclear p53 and p53-mediated response to stress; activation of p21 and p73	NSCLC (35), melanoma (36), renal cancer (37), AML (28), NHL (38), MM (32), pancreatic cancer (39), various (1)
EGFR	Reduction of cell proliferation	NSCLC (35)
RAS	Reduction of cell proliferation	NSCLC (35)
PAR-4	Nuclear retention and activation of proapoptotic effects	Pancreatic cancer (39)
p21	Reduction of cell proliferation	Renal cancer (37,40) NHL (41)
p27	Reduction of cell proliferation	MM (32), NHL (41)
FOXO proteins	Promotion of cell cycle arrest, apoptosis, and downregulation of AKT, PTEN, Wnt/β-catenin signals	CLL (30), AML (11), ovarian cancer (42), MM (32), NHL (41), pancreatic cancer (39), various (1)
BRAF	Inhibition of cell proliferation, promotion of cell cycle arrest	Melanoma (36)
pRB	Upregulation of p27; promotion of cell cycle arrest	MM (32)
APC	Downregulation of Wnt/β-catenin signals	MM (32)
eIF4E	Downregulation of capped-dependent translation of select oncogenes (e.g., Myc, CDC25A, BRD4, Bcl-2, Bcl-6, Mcl-1, Bcl-xL)	MM (32)
Topo IIα	Nuclear retention and sensitization to topoisomerase II poisons	AML (43), MM (32)

a dose-dependent growth inhibition and efficacy across multiple mutational variants in pre-clinical studies (35,45). Mutations in epidermal growth factor receptor (EGFR) and p53 have been associated with poorer outcomes (46,47). One study showed that selinexor was effective even in cells with mutations in EGFR, TP53, phosphatase and tensin homologue, RAS, and PIK3CA (35). Synergistic inhibition was also noted with the combination of selinexor and cisplatin (35). There is currently a multicenter phase I/II clinical trial of selinexor with docetaxel in previously treated KRAS-mutant NSCLC that is underway (48).

Breast cancer

Selinexor has shown promise in pre-clinical studies in triple-negative breast cancer by inducing cell apoptosis and

Table 2 List of registered clinical trials involving Selinexor in various malignancies (44)

#	NCT number	Conditions
1	NCT03193437	Thymoma
2	NCT03095612	NSCLC
3	NCT03147885	Lymphoma (various types)
4	NCT02606461	Liposarcoma
5	NCT02249091	AML
6	NCT01986348	Glioblastoma, glioma
7	NCT02402764	Breast cancer
8	NCT02227251	DLBCL
9	NCT02250885	Neuroendocrine carcinoma
10	NCT02025985	Ovarian, endometrial, cervical, breast cancer
11	NCT02530476	Leukemia
12	NCT02403310	Leukemia
13	NCT02471911	DLBCL
14	NCT02336815	MM
15	NCT02389543	MM
16	NCT02323880	Childhood CNS/solid neoplasm, lymphoma
17	NCT03466827	Thymoma
18	NCT02078349	Solid tumors
19	NCT02485535	AML, MDS
20	NCT02283359	Esophageal, gastric cancer
21	NCT02215161	Prostate cancer
22	NCT02831686	MM
23	NCT02573363	AML
24	NCT02199665	MM
25	NCT02314247	T-cell lymphoma
26	NCT02835222	AML
27	NCT02138786	Richter's transformation
28	NCT02228525	MDS
29	NCT02120222	Melanoma
30	NCT02091245	Leukemia
31	NCT02741388	B-cell lymphoma
32	NCT02212561	AML, ALL, MDS, MPAL
33	NCT03042819	Soft tissue sarcoma
34	NCT02213133	Squamous cell carcinoma
35	NCT02780609	MM
36	NCT02431351	MDS
37	NCT02384850	Colorectal neoplasm
38	NCT02186834	MM
39	NCT02299518	AML
40	NCT01607905	Solid tumor
41	NCT02351505	SCLC
42	NCT02343042	MM
43	NCT02628704	MM
44	NCT03555422	Endometrial cancer
45	NCT02146833	Prostate cancer
46	NCT03212937	T-cell lymphoma
47	NCT02536495	Squamous cell lung carcinoma
48	NCT02269293	Ovarian, endometrial cancer
49	NCT02137356	Rectal neoplasms
50	NCT02093403	AML
51	NCT02303392	Leukemia, lymphoma
52	NCT01607892	Hematological malignancies
53	NCT03071276	AML
54	NCT02178436	Pancreatic cancer
55	NCT03110562	MM
56	NCT02088541	AML
57	NCT02416908	AML
58	NCT02069730	Salivary gland cancer
59	NCT01896505	Sarcoma
60	NCT02419495	Advanced cancers

NSCLC, non-small cell lung cancer; AML, acute myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; MM, multiple myeloma; CNS, central nervous system; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; MPAL, mixed phenotype acute leukemia; SCLC, small cell lung cancer.

reduced tumor growth (33,49). One study demonstrated that selinexor increased nuclear accumulation of the anti-apoptotic protein survivin and blocked STAT3 binding to the survivin promoter (33). The overall effect is decreased

cytoplasmic levels of survivin and promotion of cell death. Currently, there are two phase II clinical trials of selinexor in patients with metastatic breast cancer.

Pancreatic cancer

The use of SINEs in pancreatic cancer remains largely in the pre-clinical setting. One study demonstrated that SINEs inhibited proliferation and promoted apoptosis of pancreatic cancer cells both *in vitro* and *in vivo* (39). Additionally, KPT-185 caused intranuclear accumulation of prostate apoptosis response-4 (PAR-4), which is a proapoptotic protein that is frequently downregulated in pancreatic cancer (39). KPT-330 in combination with gemcitabine demonstrated synergistic inhibition in pancreatic cancer cells *in vitro* (50).

Melanoma

Targeting BRAF and MEK pathways through kinase inhibition are important in the treatment of melanoma, but resistance to therapy eventually develops (8). SINE compounds induced cytostatic and pro-apoptotic effects in melanoma cell lines regardless of BRAF mutation status, as well as inhibition of tumor growth *in vivo* (36). The mechanisms of apoptosis appear to involve multiple cellular pathways involving inhibition of ERK phosphorylation, increased nuclear localization of p53 and phosphorylated MAPK, and G1/S phase cell cycle arrest (36,51). There is evidence of potential synergy between CRM1 and BRAF inhibition in BRAF-mutant melanoma (52), but this has yet to be tested in a clinical setting.

Renal cell cancer

Fewer studies on SINEs are available in RCC, but published data demonstrating growth inhibition by SINE compounds were achieved through increasing nuclear localization of p21 and p53 to induce cell apoptosis (37,40).

Gynecologic cancer

The early pre-clinical studies in ovarian cancer cells were instrumental in furthering the understanding of CRM1 inhibitors (21). Ovarian cancer cells demonstrated sensitivity to the effects of selinexor alone and in combination with cisplatin (42). The growth inhibition effect was thought to be from FOXO1 targeting, which has been implicated in platinum-resistant disease. There are currently clinical trials in ovarian and endometrial cancers.

Leukemia

The activity of SINE compounds have been studied most extensively in pre-clinical and clinical trials involving acute leukemias (7,8). CRM1 levels are frequently elevated in leukemias and have been independently associated with a worse prognosis in patients with AML (27). CRM1 inhibitors target multiple mutations that play an important role in leukemogenesis, including NPM1, TP53, CEPBA, FLT3, and cKIT (7,8). NPM1 is a phosphoprotein that shuttles between the cytoplasm to the nucleus, and mutated NPM1 delocalizes to the cytoplasm to promote leukemogenesis via a p53-regulated pathway (53). In AML cell lines, SINEs induced apoptosis regardless of NPM1 mutational status, but the presence of a p53 mutation resulted in decreased responsiveness to inhibition by KPT-185 as compared to p53 wild type cells (27). MDM2 is a p53-specific ligase that degrades p53, and inhibition of MDM2 by Nutlin-3a increases nuclear and cytoplasmic levels of p53, leading to a p53-mediated cell apoptosis. The combination of Nutlin-3a with SINEs demonstrated synergistic activity in AML cells *in vitro* (27). SINE further downregulates FLT3 and c-KIT (28), and induces blast differentiation through regulation of CEBPA (29). In studies of ALL, selinexor has similarly demonstrated robust pre-clinical activity through inhibition of BCR-ABL and other TSPs (7,8,34).

Since these studies, several phase I/II clinical trials have emerged utilizing selinexor as a single-agent (54) and in combination with various chemotherapy regimens for AML, which have reported both tolerability and overall response rates ranging from 14–70% (54-57). The most commonly reported adverse effects of selinexor are gastrointestinal symptoms of nausea and vomiting, as well as fatigue, and electrolyte abnormalities (54,56-59). Recently, a second generation XPO1 inhibitor, KPT-8602, was developed and studied in pre-clinical models of AML (60) and ALL (61). The studies report decreased CNS penetration with resultant lower rates of anorexia and weight loss while maintaining similar potent anti-leukemic activity, which appears to offer an advantage over the first-generation SINEs (60,61).

In CLL, SINEs can restore normal regulation in the dysregulated pathways of CLL and can induce apoptosis in CLL cells both *in vitro* and *in vivo* (30).

Lymphoma

Similar to acute leukemias, the activity of SINE compounds in lymphomas have worked largely through nuclear localization of p53, downregulation of c-myc and NFkB, and activating pathways leading to cell apoptosis (7,8,31,38). A phase I clinical trial in patients with relapsed or refractory non-Hodgkin's lymphoma found that selinexor was tolerable and resulted in an ORR of 31% (62). Several other early phase clinical trials in lymphoma are underway.

MM

The use of SINE compounds in MM has generated significant interest of late. CRM1 is overexpressed in MM cells, and knockdown studies showed that CRM1 is essential for MM cell viability (32). Hence, numerous pre-clinical studies followed combining SINE compounds with standard anti-MM agents that target multiple pathways, such as p53, APC, pRB, FOXO, NFkB, glucocorticoid receptor, TOP2A, and DDR (7,8,32). The consequence of CRM1 inhibition is MM cell apoptosis through activation of p53 and caspases, nuclear localization of TSPs (p53, p21, p27, Rb), downregulation of c-myc and cell cycle regulatory genes, and promotion of G1/S cell cycle arrest, just to name a few of the molecular effects (32).

There are several phase I/II clinical trials investigating selinexor in combination with other standard MM agents on patients with relapsed or refractory MM (32). Among them was one recent multicenter phase I study in heavily pre-treated patients with MM or Waldenstrom macroglobulinemia which found tolerable toxicities and an ORR of 4% when used as a single agent, and 50% when combined with dexamethasone (63). A recently published phase IIb (STORM) study of patients with refractory MM demonstrated that combining selinexor with low-dose dexamethasone achieved an ORR of 21% in quad-refractory patients and 20% in penta-refractory patients (64).

The promising future of CRM1 inhibitors

Few classes of anti-cancer agents have as broad applicability across malignancies as do the CRM1 inhibitors. This can be explained by the fact that inhibition of CRM1 targets many of the hallmark pathways of oncogenesis. Moreover, SINE compounds can be easily combined with existing standard regimens for various malignancies and have been generally well tolerated in multiple early phase clinical trials. While SINE compounds as a single agent have not demonstrated adequate potency in the clinical setting (54,63), their use in combination with existing regimens or agents have often demonstrated synergistic effects across multiple malignancies (35,50,52,55-57,63,64). Karyopharm Therapeutics is currently conducting a pivotal randomized phase III (BOSTON) study combining bortezomib, selinexor, and dexamethasone in patients with refractory MM, based on phase I/II data from the STORM study. There may even be a role in for SINE compounds in combination with immunotherapy agents or cell-based therapies, although no studies are being conducted to date. However, the gastrointestinal toxicities of selinexor have been observed as a limitation to dose escalation (54). This sets the stage for further investigation into the second-generation SINE compound KPT-8602 that may improve upon selinexor (60,61). KPT-8602 offers a 30-fold less penetration across the blood-brain barrier, while maintaining similar pharmacokinetic properties to selinexor. In mice models, this resulted in less anorexia, malaise, and weight loss as compared to selinexor, suggesting that KPT-8602 can offer a better tolerability profile while maintaining comparable efficacy (60,65). Additionally, because SINEs act through covalent binding to the exportin, mutations in the Cys528 residue can render CRM1 resistant to the SINEs, as was found in fungi (6). Hence, the development of CRM1 inhibitors that can bind in a non-covalent fashion is worth investigating as a strategy to overcome this resistance (6). The potential of SINE compounds to dramatically impact treatment outcomes is promising, but it remains to be seen how they will fare in larger clinical trial settings.

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Footnote

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