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Selective inhibitors of nuclear export (SINE)– a novel class of anti-cancer agents

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Abstract

Dysregulation of the nucleo-cytoplasmic transport of proteins plays an important role in carcinogenesis. The nuclear export of proteins depends on the activity of transport proteins, exportins. Exportins belong to the karyopherin β superfamily. Exportin-1 (XPO1), also known as chromosomal region maintenance 1 (CRM1), mediates transport of around 220 proteins. In this review, we summarized the development of a new class of antitumor drugs, collectively known as selective inhibitors of nuclear export (SINE). KPT-330 (selinexor) as an oral agent is showing activities in early clinical trials in both solid tumors and hematological malignancies.

Keywords: SINE, KPT-330, Selinexor, Nuclear export

Introduction

The nucleo-cytoplasmic transport of proteins plays an important role in maintaining normal cellular functions. The nuclear export of proteins depends on the activity of transport proteins, exportins. Exportin-1 (XPO1), also known as chromosomal region maintenance 1 (CRM1), mediates transport of around 220 proteins [1-4]. XPO1 is the sole nuclear exporter of several tumor suppressor (TSP), growth regulatory (GRP) proteins. These include p53, p21, p73, Rb1, apc, bcr-abl, FOXO and STAT3. Under physiological conditions, the export of these proteins prevents them from overacting in the absence of DNA injury or other oncogenic activities [5,6]. In cancerous cells, however, this export of proteins inhibits their tumor suppressor activity and promotes tumorigenesis [6,7]. Many hematologic and solid tumor malignancies have elevated XPO1 levels [8-12]. Therefore, inhibiting XPO1 can be a potential treatment option. In this review, we will discuss a new class of potential antitumor drugs, collectively known as selective inhibitors of nuclear export (SINE). These agents can block the export of TSPs and GRPs, thus maintaining their intranuclear concentration and exert anti-cancer activity.

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Nucleo-cytoplasmic transport and its inhibition by SINE compounds

XPO1 binds to the cargo proteins through a leucine rich nuclear export signal (NES) and transports the proteins through a membrane pore complex via a Ran-GTP gradient [13-15] (Figure 1). Several small molecule inhibitors of XPO1 are being studied. These include Leptomycin B (LMB), ratjadone, goniothalamin, N-azolylacrylates, anguinomycin, and CBS9106 [16-21]. They bind covalently to the cysteine residue (Cys528) in the NES binding groove of XPO1 [18]. This binding irreversibly inactivates XPO1, leading to intranuclear accumulation of TSPs and GRPs. Of these, leptomycin B (LMB) has been studied most extensively in various cancer cell lines and murine xenograft tumor models.

A phase 1 study of an XPO1 inhibitor showed only modest efficacy and severe dose limiting toxicity (e.g. malaise, anorexia, vomiting and nausea) [22]. The clinical trial was therefore discontinued. KOS-2462, a semisynthetic LMB derivative showed activity in mouse xenograft models without inducing significant toxicity [16]. CBS9106 is another small molecule oral reversible inhibitor of XPO1. It induced growth inhibition in several cancer cell lines [17]. Neither KOS-2462, nor CBS9106 have entered clinical trials.

Subsequently, several novel inhibitors of XPO1, collectively known as SINE compounds, have been developed. These compounds include KPT-330 (selinexor), KPT-335 (verdinexor), KPT-185, KPT-276, and KPT-251. Of these,

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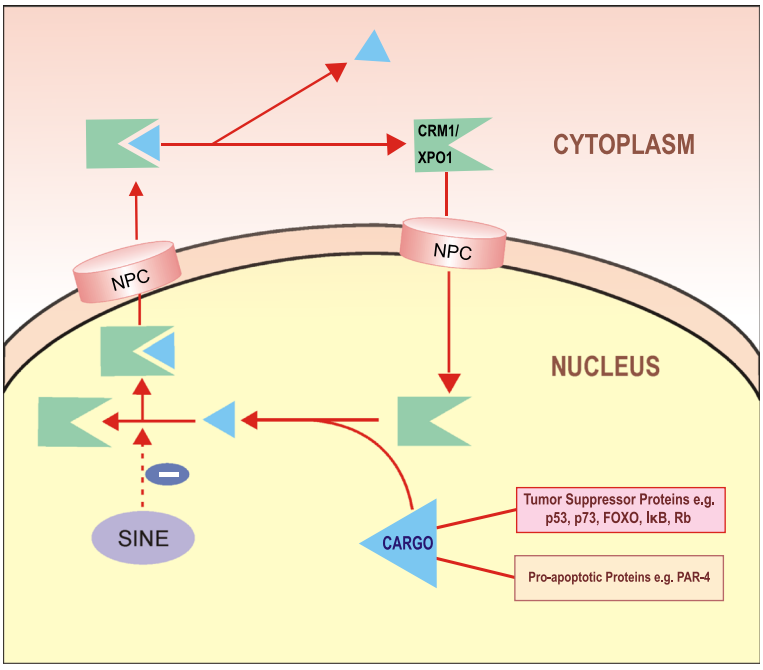


Figure 1 Mechanism of action for selective inhibitors of nuclear transportation. In the nucleus, RanGTP and cargo (tumor suppressors, pro-apoptotic proteins, etc.) form a complex with CRM1/XPO1. This complex is exported through the nuclear pore complex (NPC) to the cytoplasm. CRM1 is then recycled back to the nucleus for another round of export. Selective inhibitors of nuclear export (SINE) binds to CRM1/XPO1 and blocks the protein export, and therefore the cargo proteins are retained in the nucleus, leading to growth inhibition.

KPT-185 is the most studied compound *in* vitro with most potency. However, its use *in vivo* is limited by poor pharmacokinetics [23-25]. KPT-330 is nearly as potent as KPT-185 and has acceptable oral bioavailability. KPT-251 and KPT-176 are not as potent as KPT-185 but are bioavailable orally [23-25]. These agents are currently undergoing clinical trials for several solid and hematologic malignancies including breast, colon, pancreas, renal, multiple myeloma (MM), mantle cell leukemia (MCL), chronic lymphocytic leukemia (CLL), and acute myeloid leukemia (AML).

SINE in pancreatic cancer

KPT-127, KPT-185, KPT- 205, and KPT-227 were studied in pancreatic cancer cell lines [26]. Prostate apoptosis response-4 (PAR-4) is a proapoptotic protein in the nuclear and cytoplasmic compartments. PAR-4 translocates to the nucleus via XPO1 in external stress conditions to cause apoptosis [27]. PAR-4 is downregulated in pancreatic cancers. Downregulation of PAR-4 directly correlates to worsening outcomes in pancreatic cancer [28]. KPT-185 was shown to increase intranuclear PAR-4 without interfering with its import from the cytoplasm. It also induced PAR-4 phosphorylation, thus activating it and leading to apoptosis. Active SINEs had a median inhibitory concentration (IC_{50}) of 150 nmol/L and inhibited pancreatic cancer cell lines while sparing normal human pancreatic ductal epithelial cells. The *in vivo* effects were noted using KPT-330 (selinexor) in subcutaneous and orthoptic pancreatic cancer models in mice. Oral administration of KPT-330 led to significant tumor growth inhibition when compared with control or gemcitabine treatment [26]. KPT-330 treated mice had drastic reductions in tumor size as compared with controls. Thus, pre-clinical studies of CRM1 inhibition using SINE compounds revealed an attractive novel treatment of pancreatic cancer.

SINE in triple-negative breast cancer (TNBC) (ER^-, PR^-, $Her2^-$)

Overexpression of survivin is associated with poor prognosis in breast cancer [29]. Survivin inhibits apoptosis by stabilizing X linked inhibitor of apoptosis (XIAP) in the cytoplasm [30]. Survivin expression is also directly affected by STAT3, a member of Janus-activated kinase (JAK)/STAT [31], which is increased in several malignancies including TNBC [32]. Cytoplasmic localization is required for survivin to inhibit apoptosis [30]. XPO1 mediates transport of survivin and STAT3 to the cytoplasm, and inhibits apoptosis [33,34]. Inhibition of XPO1 blocked STAT3 binding to survivin promoter and decreased survivin expression. In the meanwhile, it was shown that survivin was cleaved by caspase-3, therefore leading to overall decrease of survivin level [4]. In the

study, it was shown that KPT-185, KPT-251 and KPT-276 inhibited tumor cell growth and enhanced apoptosis *in vitro* in 3 different cell lines. KPT-185cis had the lowest IC_{50}. KPT-330 had profound effects on tumor cell growth inhibition and apoptosis with an IC_{50} ranging from 5 to 21 nmol/L. The data suggested that twice weekly dosing of KPT-330 at 25 mg/kg for 42 days significantly reduced tumor growth when compared to control or standard treatment with 5-fluorouracil (P = 0.011). It was determined that XPO1 inhibition caused nuclear retention of survivin which was then degraded by caspase-3 [4]. Survivin transcription was also shown to be repressed by inhibition of CREB binding protein (CBP) mediated STAT3 transactivation.

This study expands the role of SINEs in treatment of breast cancer and other solid tumors. KPT-330 is currently undergoing phase I clinical trial in advanced solid tumors [35]. In this early trial, KPT-330 was administered orally for 8–10 doses in a 28-day cycles to 103 patients (59/44 M/F; median age 61 years) across 12 dose levels. Dose limiting toxicites (DLT) (fatigue, dehydration, nausea) were noted. Dosing at 65 mg/m^2 BIW is ongoing since maximal tolerated dosage (MTD) was not reached yet at the time of the report. There were 87 evaluable patients (pts) for response. Among them, there were 3 PR in colorectal cancer (KRAS mutant), melanoma (BRAFwt) and ovarian adenocarcinoma pts. Stable disease (SD) was seen in 39 pts, with 12 pts lasting over 6 months. All 5 evaluable pts with hormone and chemotherapy refractory prostate cancer (HRPC) achieved SD; Nine of 13 evaluable pts with squamous head and neck cancer had SD diseases. Further evaluations are ongoing.

SINE in non-small cell lung cancer (NSCLC)

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) are main treatment for patients with advanced NSCLC with EGFR exon 19 deletion or exon 21 substitution [36,37]. EGFR overexpression and p53 mutations are associated with poor outcomes in NSCLC [38,39]. As mentioned earlier, nuclear export of p53 is mediated by XPO1 [40]. Sun *et al.* studied the antitumor activity of KPT-330 against NSCLC *in vitro* and *in vivo*, and concluded that the antitumor activity of KPT-330 against NSCLC was independent of p53 mutational status [41]. The antitumor activity of KPT-330 against NSCLC was likely related to p73. p73 shares structural and functional similarities with p53 and cooperates with p53 to induce apoptosis [42]. In cells with mutant p53, p73 is shown to cause apoptosis via activation of p53-inducible genes [42]. KPT-330 caused dose-dependent growth inhibition of NSCLC with correlating decrease in XPO1 levels [41]. Moreover, KPT-330 can inhibit NSCLC cell growth even in EGFR-TKI resistant cancer cells. Combination of KPT-330 and cisplatin displayed synergistic *in vitro* antiproliferative activity. *In vivo* treatment of mice with a dose of 10 mg/kg, thrice weekly for 4 weeks showed significant tumor growth inhibition with minimal toxicities. Another independent study confirmed the above findings using KPT-185 *in vitro* and its oral clinical equivalent KPT-276 on NSCLC cells *in vivo* using mouse xenografts [43].

SINE in renal cell carcinoma (RCC)

Despite several approved drugs for metastatic RCC, the progression free survival remains only 1 to 2 years [44]. KPT-185 was studied *in vitro* in RCC cell lines [45]. XPO1 is overexpressed in high grade RCC. KPT-185 and its oral equivalent KPT-251 decreased XPO1 levels. They also compared SINE with sorafinib and found greater inhibition of tumor growth with KPT-251 at a higher dose of 75 mg/kg in mouse xenografts (p = 0.07) without any adverse effects. KPT-185 increased nuclear localization of p53 and its downstream protein p21 to cause cell cycle arrest. Also, cytosol p21 reduction leads to apoptosis. KPT-251 showed increased p53 and p21 nuclear levels *in vivo.* Sorafinib, on the other hand, decreased nuclear and cytoplasmic p21, thereby causing apoptosis [46]. These findings warrant further clinical studies using SINE as a treatment choice in RCC.

SINE in melanoma

BRAF kinase activation is present in about 50% of melanomas [47-52]. Treatment with BRAF and MEK inhibitors has been very successful, but the eventual development of resistance to these kinase inhibitors calls for more agents [51,53-60]. XPO1 expression is found to be increased in metastatic melanoma more than primary melanoma or nevi [61]. Hence, SINE can be a potential treatment for metastatic melanoma. Salas Fragomeni *et al.* conducted *in vitro* and *in vivo* studies in metastatic melanoma using SINE and BRAF inhibitors [62]. They concluded that BRAF inhibition by PLX-432 led to inhibition of cell proliferation in BRAF-mutant cell lines, but BRAF wild-type (WT) melanoma cell lines were relatively resistant [53,54]. However, SINEs inhibited cell proliferation and caused cytotoxicity across all cell lines, regardless of BRAF status. They also showed synergistic activity between SINE and PLX-432 in BRAF mutant melanoma. Furthermore, SINE and MEK inhibitors were also able to synergize with the three-way treatment (SINE/MEK/BRAF), achieving an even lower IC_{50}. SINE also caused G1/S phase cell cycle arrest, another effect synergized with concomitant BRAF inhibition in BRAF mutant cell lines. SINE also increased nuclear p53, retinoblastoma (Rb). An increase in ERK phosphorylation in the nucleus was also noticed. ERK phosphorylation has been linked to increased cellular proliferation and development of chemoresistance [61,63,64]. However, this SINE- induced ERK phosphorylation was

prevented in the presence of BRAF inhibition, possibly explaining the synergy between these two compounds. *In vivo* mouse model showed complete tumor regression using the combination regimen [62].

SINE in acute leukemia

SINE compounds have been studied as a novel anticancer strategy in multiple preclinical trials of hematologic malignancies. Higher levels of XPO1 are associated with poor prognosis in acute leukemia [65]. Earlier preclinical work demonstrated that KPT-185 inhibited proliferation and induced G1 phase cell cycle arrest in AML cell lines and primary AML blasts *in vitro* [25]. Nucleophosmin 1 (NPM1) is a nucleolar TSP that shuttles between the nucleolus and cytoplasm via the XPO1-RanGTP pathway and regulates p53 dependent cell death [66]. NPM1 mutations in AML cells were seen in 25% to 35% cases [67]. These mutations cause increased XPO1 binding and localization of NPM1 in the cytoplasm [68]. SINEs block this export of mutant NPM1 and induce antileukemic effects in AML cell lines and primary AML blasts. AML blasts with NPM1 mutations were very responsive to KPT-185 and had an IC_{50} of 100 nmol/L. However, wild type (WT) NPM1 in AML cells were also sensitive to SINEs, indicating that other TSPs like p53 also have a role in the antileukemic effects of SINE. Kojima *et al.* further established that p53 is a major determinant in SINE induced cytotoxicity in AML, independent of NPM1. Mutant p53 samples were less sensitive to KPT-185 [65]. XPO1 inhibition by SINE also resulted in blast differentiation, likely due to upregulation by p53 and CEBPA [69], a protein essential for myeloid granulocytic differentiation via activation of several necessary genes [70,71]. SINEs were also shown to downregulate FLT3 and cKIT tyrosine kinase proteins [25]. FLT3 gene mutation may coexist with NPM1 mutations [72]. SINE downregulated FLT3 and NPM1. Thus, SINEs can potentially target 2 critical pathways. cKIT mutations or overexpression also confer a worse prognosis in AML [73,74]. Kojima *et al.* demonstrated synergistic activity using the combination of SINE with MDM2 inhibitor Nutlin-3a. MDM2, frequently overexpressed in AML, is a p53-specific ligase, promoting p53 degradation [75]. Nutlin-3a is a selective MDM2 inhibitor, shown to increase nuclear and cytoplasmic p53 and induces p53 mediated apoptosis [75]. The addition of SINE to Nutlin-3a led to higher p53 nuclear level than by using either agent alone *in vitro* [65]. This combination strategy can be potentially effective not only in AML but in several other malignancies. Furthermore, SINEs are not shown to induce apoptosis in normal hematopoietic cells [23,65,76].

T cell-acute lymphoblastic leukemia (T-ALL) is fatal in about 50-70% of adult patients [77-79]. SINE has shown striking activity in preclinical study for treatment of T-ALL. KPT-185 and KPT-330 showed rapid apoptosis induction in T-ALL cell lines *in vitro* with acceptable IC_{50} [76]. *In vivo* treatment showed minimal gastrointestinal adverse effects.

Philadelphia chromosome positive ALL remains a challenge even with availability of multiple tyrosine kinase inhibitors [80,81]. Walker *et al.* demonstrated successful use of KPT-185 *in vitro* and KPT-330 *in vivo* in Philadelphia chromosome positive ALL (Ph + ALL) and chronic myeloid leukemia blast crisis (CML-BC). Combination with imatinib led to synergistic effects [82]. SINE treatment was associated with significant reduction in BCR-ABL + cells in mice, likely by reactivation of the tumor suppressor proteins PP2A, p53, p21 and FOXO3a [82].

The preliminary results of an ongoing phase I trial using KPT-330 in relapsed/refractory AML were presented Yee *et al.* recently. They showed that KPT-330 treatment given to heavily pretreated, refractory/relapsed AML patients had no DLT. Out of the 32 evaluable patients, 4 (12%) showed complete response (CR) with hematological recovery, 1 (3%) showed marrow CR (mCR), mCR without hematological recovery was seen in 1 (3%) patient. Partial response (PR) was seen in 2 patients (6%). Eleven patients (34%) showed progression while 12 (37%) experienced stable disease after 30 days [83].

SINE in chronic leukemia

Even though more options are available now for chronic lymphocytic leukemia (CLL) therapy, p53 positive CLL still has poor prognosis [84-91]. Preclinical study by Lapalombella *et al.* using KPT-185 *in vitro* and KPT-251 *in vivo* showed promising results in chronic lymphocytic leukemia (CLL) cells [24]. KPT-185 induced nuclear retention of IκB. IκB is an endogenous inhibitor of the inflammatory antiapoptotic transcription factor NFκB, which is involved in the upregulation of MCL1, the most significant antiapoptotic protein associated with CLL [92,93]. KPT-185 induced MCL1 depletion, likely due to inactivation of NFκB by nuclear retention of IκB. Murine xenografts treated with KPT-251 showed significant improvement in survival when compared with fludarabine [24]. In a 37 year old patient with CML-AP resistant to multiple treatment options (TKIs, interferon, omacetaxine and azacitidine), a trial of selinexor (KPT-330) on a compassionate use protocol showed significant reduction in bone pain, spleen size, white blood cell count, and lactate dehydrogenase (LDH) level. Peripheral blood smears showed a dramatic reduction in immature myeloid blasts [82].

SINE in multiple myeloma (MM)

SINE was shown to induce cytotoxicity and inhibits osteoclastogenesis in multiple myeloma *in vitro* and *in vivo* [12]. High CRM1 expression was found to be associated with lytic bone disease ($P = 0.008$) and shorter

survival (P = 0.024). CRM1 levels are higher in bortezomib resistant MM cells. SINEs caused nuclear accumulation of multiple TSPs including p53, FOXO3a, IκB, p21 and PP2A. SINE also caused anti-MM effects in the bone marrow microenvironment by activating caspase cascade and causing PARP cleavage, and showed a synergistic effect when combined with bortezomib, without affecting bone marrow stromal cells. Another study, however, observed no synergy with KPT-276 in combination with dexamethasone, bortezomib, or melphalan [94]. Osteoclastogenesis is controlled by NFκB activation through cytokine RANKL and NFAT1c. Both KTP-185 and KPT-330 blocked RANKL mediated activation of NFκB in osteoclast (OC) precursor cells, and also blocked NKFAT1c, which is also essential for osteoclast function [12,94]. Surprisingly, SINE reduced the expression of oncogene c-myc, despite the fact that CRM1 does not mediate c-myc export [95]. C-myc activation is associated with poor prognosis and shorter survival in monoclonal gammopathy of undetermined significance (MGUS) and MM [96]. A study done in 2012 indicated that p53 activation is responsible for inhibiting CRM1 and c-myc genes [97]. BRD4, another gene downregulated by SINE, regulates DNA replication, promotes c-myc transcription and is associated with MM disease progression [98,99]. BRD4 knockdown causes cell cycle arrest and subsequent apoptosis [98]. JQ1, a small molecule inhibitor of BRD4 gene causes decreased transcription of c-myc, an effect that was synergistic with KPT-276 [98]. This result can be utilized for further cytotoxic treatment of tumor cells in MM. Lastly, 2 week *in vivo* treatment with KPT-276 had a comparable effect on M-spike reduction with melphalan and bortezomib, the two potent anti-MM drugs [94].

SINE in lymphoma

Novel agents and regimens for lymphoma are moving rapidly from bench to bedside [89,100-104]. KPT drugs have been studied preclinically for the treatment of resistant mantle cell lymphoma (MCL). Yoshimura *et al.* conducted an in vitro study of KPT-185 in MCL and showed that SINE increases MCL cell apoptosis primarily by increasing nuclear p53 levels [105]. They verified that KPT-185 downregulated c-myc and NFκB, thus targeting multiple pathways of apoptosis. Zhang *et al.* studied the *in vivo* effects of KPT-276 in mice and showed marked activity with minimal weight loss, gastrointestinal side effects, or myelosuppression [106]. London *et al.* studied SINEs *in vivo* in a phase I clinical trial in spontaneous canine NHL, osterosarcoma or mast cell tumor. They used KPT-335 at a dose of 1 mg/kg to 1.75 mg/kg two times a week and showed significant response without development of serious side effects [107]. Gutierrez *et al.* presented the findings of their phase I study with KPT-330 in 32 pretreated refractory lymphoma patients. The optimal dosing of KPT-330 is at least 45 mg/m^2 and durable activity of KPT-330 was observed in those NHL patients [108]. These data further validated the activity of SINEs in human malignancies.

Future directions

More and more targeted small molecule inhibitors are entering clinical application quickly [53,84,85,109-113]. Selective inhibitors of nuclear export (SINE) show activity in a wide variety of cancers, both hematologic and solid tumors [114,115]. Currently, they are being studied in early phase clinical trials (Table 1). Their low toxicity profile and synergistic effects in combination with other antineoplastic agents support further development in

Table 1 Selinexor (KPT-330) in clinical trials

Diseases	Trial	Recruting status	NCT number
Relapsed ALL and AML	Phase I	Recruiting	NCT02091245
Unresectable melanoma	Phase I	Not yet Recruiting	NCT02120222
Gynaecologic malignancies	Phase II	Recruiting	NCT02025985
Advanced/metastatic solid tumors	Phase I	Recruiting	NCT02078349
Soft-tissue or bone sarcoma	Phase Ib	Recruiting	NCT01896505
Advanced/metastatic solid tumors	Phase I	Recruiting	NCT01607905
Metastatic resistant prostate cancer	Phase II	Recruiting	NCT02146833
Advanced hematological malignancies	Phase I	Recruiting	NCT01607892
Recurrent glioblastoma	Phase II	Recruiting	NCT01986348
Relapsed/refractory AML	Phase II	Rectruiting	NCT02088541
Refractory/relapsed CLL	Phase II	Recruiting	NCT02138786
Acute myeloid leukemia	Phase I	Recruiting	NCT02093403
Locally advanced rectal cancer	Phase I	Not yet Recruiting	NCT02137356

Note: details of all NCT trials can be found on www.clinicaltrials.gov.

combination regimens against a wide range of malignancies. SINEs represent a unique, novel class of targeted agents for various malignancies.

Competing interest
The authors have no relevant competing interest.

Authors' contributions
DL and KP designed the study. All authors have contributed to data preparation, drafting and revising the manuscripts. All authors have read and approved the final manuscript.

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