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Nucleocytoplasmic transport in gynaecological cancer: From mechanisms to therapeutic potential (Review)

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Abstract. Proper localization of proteins and RNAs in a cell is crucial for physiological function and cellular homeostasis, while disruption of the nucleocytoplasmic transport machinery leads to carcinogenesis. In gynaecological (endometrial, cervical and ovarian) tumours, upregulated nuclear transport protein expression promotes malignant cell proliferation, invasion and resistance to therapy. Therefore, therapeutic targeting of nuclear transport proteins has emerged as a promising anticancer approach. Researchers have extensively studied both nuclear import and export inhibitors in preclinical settings, alone or in combination with other targeted therapy agents. However, to date, only one compound, the exportin 1 inhibitor Selinexor, has been approved for cancer treatment. The development of nuclear transport inhibition-based therapies is hindered by limited inhibitor specificity and complex cellular resistance mechanisms. The aim of the present review was to clarify the connection between nuclear transport dysregulation, hallmarks of gynaecological tumours and the challenges of inhibiting nuclear transport in gynaecological cancer treatment.

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Abbreviations: ABC, ATP-binding cassette; FDA, Food and Drug Administration; LMB, leptomycin B; MDR, multidrug resistance; NE, nuclear envelope; NES, nuclear export signal; NLS, nuclear localization signal; NPC, nuclear pore complex; Nup, nucleoporin; P-gp, P-glycoprotein; SINE, Selective Inhibitors of Nuclear Export; TME, tumour microenvironment; TSP, tumour suppressor protein

Key words: nucleocytoplasmic transport, endometrial cancer, cervical cancer, ovarian cancer, nuclear transport inhibitors

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1. Introduction

Nuclear alterations accompany a variety of cellular processes, including cell differentiation (1), senescence (2), infection (3,4) and diseases such as laminopathies (5) and cancer (6). In cancer, changes in nuclear morphology are linked to carcinogenesis, as they facilitate tumour development and may increase genetic diversity (7-9). In addition to nuclear morphological changes, cancer frequently shows dysregulated nuclear transport. Mutations, post-translational modifications and changes in nuclear transport protein expression contribute to malignancy by activating cancer-related signalling pathways and promoting hallmarks of cancer, including cell proliferation, invasiveness and resistance to therapy (10).

Gynaecological cancer comprises malignancies arising in the female reproductive system. Uterine (endometrial), cervical and ovarian cancers are the three most common types, although vaginal and vulvar cancers are also included in this category (11). Globally, gynaecological cancers account for ~15% of all cancers affecting women (12). In the context of nuclear alterations, gynaecological cancers are no exception. In the Papanicolaou smear test, cervical cancer cells are distinguished from healthy cells by nuclear irregularities (13). Nuclear alterations in size, shape, chromatin condensation and/or nuclear protein expression have also been identified in ovarian and endometrial cancer cells (14-16).

Inhibition of nucleocytoplasmic transport has emerged as a promising therapeutic strategy for a range of cancers. The first nuclear export inhibitor, Selinexor, received clinical approval for multiple myeloma and diffuse large B-cell lymphoma in 2019 and 2020, respectively (17,18). However, a comprehensive summary of recent findings in gynaecological cancers remains unavailable. Therefore, the present review highlights the role of dysregulated nuclear transport in gynaecological tumour progression and its therapeutic potential.

2. Principles of nuclear transport in eukaryotic cells, nuclear pore complex (NPC) structure and function

A defining characteristic of eukaryotic cells that distinguishes them from prokaryotic cells is the compartmentalisation of genetic material within the nucleus. The nuclear envelope (NE), a double lipid bilayer membrane, separates gene transcription and translation into distinct subcellular compartments, namely the nucleus and cytoplasm. Nuclear pores, protein-lined channels within the NE, also known as NPCs, mediate the regulated transport of macromolecules, including proteins and micro (mi)RNAs, into and out of the nucleus, thereby maintaining cellular homeostasis (19). Dysregulation of nucleocytoplasmic transport, defined as the regulated movement of macromolecules between the nucleus and cytoplasm, contributes to oncogenesis, including in gynaecological cancers, by altering the localisation of tumour suppressors, oncogenes and cell-cycle regulators (20-22). NPCs are large aqueous channels within the NE that serve as gateways for macromolecules entering and leaving the nucleus by bridging the inner and outer nuclear membranes and maintaining a selective and continuous exchange between the nucleus and cytoplasm.

The overall structure of the NPC comprises cytoplasmic filaments located on the cytosolic side of the NE, a nuclear basket on the nucleoplasmic side and ring-like structures surrounding a central transport channel (Fig. 1). These ring-like structures are subdivided into four rings: The cytoplasmic ring on the cytoplasmic side, the inner ring embedded within the NE, the nuclear ring associated with the inner nuclear membrane and the luminal ring situated within the NE lumen at the site of membrane fusion. The cytoplasmic and nuclear rings are largely identical and both contain characteristic Y-shaped assemblies known as Y-complexes. The number of NPCs varies by cell type and cell-cycle stage, with vertebrate cells typically containing ~1,000 NPCs. NPCs assemble from multiple copies of ~30 distinct proteins, called nucleoporins (Nups). In humans, the genome encodes 34 Nups, although the number varies among species (20,23).

The central Nups form a cylindrical structure with eightfold rotational symmetry and twofold rotational symmetry along the axis parallel to the nuclear envelope. This symmetrical core encircles the central transport channel and serves as a scaffold to which specific Nups attach on the cytoplasmic and nuclear sides of the NE, forming the cytoplasmic filaments and nuclear basket, respectively (23,24). The central scaffold contains Nups that harbour intrinsically disordered phenylalanine (F) and glycine (G) repeats. These molecules, known as FG-Nups, are relatively hydrophilic and essential for the NPC permeability barrier (19). Alterations in the FG-Nup-mediated permeability barrier of the NPC may promote cancer progression by enhancing oncogenic nuclear signalling, amplifying hormone-dependent transcription and supporting cellular adaptation to genomic stress and therapy (25-27). In several types of cancer, including gynaecological cancers, FG-Nups are mutated or overexpressed, altering transport selectivity and kinetics (22,28).

FG-Nups, together with transport receptors and components of the cytoplasmic filaments and nuclear basket, play crucial roles in nucleocytoplasmic transport (29,30). Cytoplasmic filaments participate in the recruitment of transport factors and are involved in the final stages of protein and mRNA export (31). The nuclear basket serves as a docking site for nuclear transport and is essential for processing and sorting molecules as they pass through the NPC. The cytoplasmic and nuclear rings function as anchors between the NPC and the NE. These rings bind the nuclear membrane, connect to the inner ring through Nup155 and provide docking sites for the recruitment of asymmetrical Nups, such as Nup358, the principal component of the cytoplasmic filaments (20,32). Studies have identified Nup155 as a notable oncogenic biomarker associated with disease progression, therapeutic response and immune evasion in various cancers, including gynaecological malignancies, whereas upregulation of Nup358 promotes tumour cell proliferation and invasion, highlighting its role in cancer progression (33-36). Each Nup performs a distinct function. FG-Nups form the diffusion barrier and/or interact with transport factors; scaffold Nups provide structural support for the NPC; transmembrane Nups anchor the complex within the membrane; and linker Nups connect different scaffold elements. Individual Nups may also perform multiple functions and occupy different locations within the NPC. A detailed description of Nup organisation has been reviewed elsewhere (19,20).

It is generally accepted that molecules <40 kDa can freely diffuse through the NPC, whereas larger molecules cannot cross the NE independently (24). The two major components of the nuclear transport machinery, the karyopherins and the Ran system, work together to transport cargo through the NPC between the nucleus and the cytoplasm. Karyopherins, comprising importins and exportins, are the principal cargo receptors that interact with NPCs, recognise transport motifs and bind cargo in a GTP/GDP-sensitive manner (37,38). The two classes of karyopherins, karyopherin α and karyopherin β (importin α and importin β), mediate cargo import into the nucleus. Members of the importin β superfamily function in concert with the small Ras-like GTPase Ran. They contain a RanGTP-binding domain at the N-terminus and multiple short α-helical HEAT repeats that mediate interactions with transport cargoes and NPCs (39). GTP binding and hydrolysis, which generate RanGTP and RanGDP complexes, direct cargo transport through NPCs (38). The asymmetric distribution of RanGTP, which is abundant in the nucleus, and RanGDP, which is abundant in the cytoplasm, drives the movement of cargo-receptor complexes through the NPC. Importin β associates with import cargoes either directly or through adaptor proteins such as importin α. These adaptors are specialised cargoes that contain N-terminal domains known as importin β-binding domains (40,41).

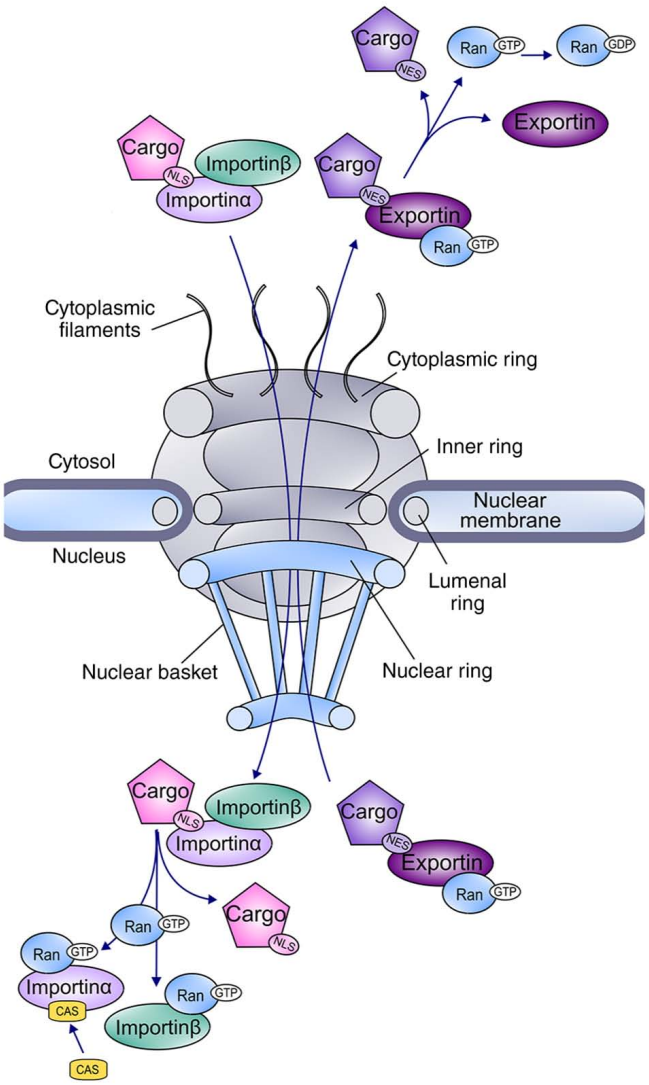

Figure 1. Primary structure of the NPC and a schematic overview of Ran-mediated nucleocytoplasmic transport. The NPC is embedded in the NE. The primary structure of the NPC consists of cytoplasmic filaments, a nuclear basket and a central core that is composed of four rings: the cytoplasmic ring on the cytosolic side, the inner ring, the nuclear ring on the inner nuclear membrane, and the lumenal ring residing in the lumen of the NE. The assembly of a trimeric import complex in the cytoplasm is required for the import of proteins bearing NLS. The nuclear proteins importin α and importin β form a complex; importinα engages the NLS of cargo proteins, and the complex travels through the NPC into the nucleus, where RanGTP binding releases it. The export of cargo proteins harbouring the NES sequence is initiated by exportin binding and is facilitated by RanGTP. After exportin binds RanGTP and a NES-harbouring cargo protein, the complex travels into the cytosol, where GTP hydrolysis to GDP causes the export complex to disassemble. NES, nuclear export signal; NLS, nuclear localization signal; NPC, nuclear pore complex; NE, nuclear envelope.

The Ran-mediated nuclear transport pathway is among the most frequently dysregulated transport systems in cancer (42) and underlies canonical nucleocytoplasmic transport by regulating cargo interactions with importins and exportins, as well as the directionality of nuclear import and export. This pathway involves binding of the importin β-importin α complex to the nuclear localisation signal (NLS) of cargo proteins, facilitating passage through the central channel of the NPC (Fig. 1). At the nuclear side of the NPC, RanGTP binding promotes cargo release into the nucleoplasm. Subsequently, RanGTP-CAS-importin α and RanGTP-importin β complexes are exported to the cytoplasm, where GTP hydrolysis leads to their dissociation. Similarly, exportin 1 (XPO1) mediates nuclear export by binding cargo proteins containing a nuclear export signal (NES) in a RanGTP-dependent manner. The resulting export complexes are transported to the cytoplasm, where GTP hydrolysis triggers complex disassembly (23,32). Dysregulation of the classical Ran pathway has been implicated in cancer, with elevated Ran expression associating with aggressive tumour phenotypes and increased cellular dependence on Ran for survival (43-45).

Beyond their established role in nucleocytoplasmic transport, NPCs also perform transport-independent functions. Increasing evidence indicates that NPCs contribute to gene regulation and chromatin organisation through mechanisms unrelated to molecular transport. Nups participate in genome architecture, transcriptional complex assembly, chromatin structure regulation and the coordination of transcription with nuclear transport processes (46).

3. Alterations in nuclear transport in gynaecological cancer cells

Nuclear transport can be dysregulated at several levels in cancer cells, including modifications of cargo proteins and transport receptors, altered expression of nuclear transport components and changes in nuclear pore number.

The translocation of cargo from the cytoplasm to the nucleus may be facilitated by direct post-translational modification of the cargo itself or by modification of inhibitory proteins that normally mask nuclear localisation sequences. An example is the nuclear translocation of β-catenin in the canonical Wnt signalling pathway. Wnt/β-catenin signalling promotes the proliferation, migration and stem-like characteristics of endometrial (47), ovarian (48) and cervical cancer cells (49). In the absence of Wnt ligands, cytoplasmic β-catenin undergoes phosphorylation, ubiquitination and subsequent proteasomal degradation. Wnt signalling activation suppresses these modifications, allowing β-catenin to accumulate and translocate to the nucleus, where it activates target gene expression. In gynaecological cancers, mutations in the β-catenin gene, *CTNNB1*, may also result in constitutive nuclear localisation of the protein (50).

Modification of cargo inhibitors is central to NF-κB signalling. Members of the NF-κB transcription factor family promote cancer cell proliferation, survival, metastasis, metabolic reprogramming and inflammation (51). Although NF-κB activity may be suppressed during the early stages of human papillomavirus infection to facilitate immune evasion (52), persistent NF-κB activation subsequently promotes malignant transformation and is positively associated with cervical cancer progression (53). In its inactive state, NF-κB is retained in the cytoplasm through association with its inhibitor, IκB. After pathway activation, IκB kinase phosphorylates IκB, which is ubiquitinated and degraded by the proteasome. This releases NF-κB, which karyopherin β1 (KPNB1) transports into the nucleus, where it binds DNA and activates gene transcription. Within the nucleus, NF-κB activity is further regulated by phosphorylation (54), acetylation (55), sumoylation (56) and other post-translational modifications. Nuclear accumulation

of NF-κB has been observed in cervical cancer and is associated with disease progression (57). Conversely, some studies have linked nuclear localisation of NF-κB with ovarian cancer regression (58).

Post-translational modifications and mutations that alter the localisation of nuclear transport receptors have not been extensively investigated in gynaecological cancers. In other malignancies, however, such alterations have been well documented. For example, acetylation of karyopherins in lung cancer alters their subcellular localisation and disrupts nuclear transport (59). Leukaemia has been associated with Nup translocations and fusion events involving HOX transcription factors and other genes (60-63). In B-cell lymphoma, the E571K point mutation in XPO1 alters its localisation and affinity for negatively charged cargoes (64,65) and increases cellular sensitivity to nuclear transport inhibitors (66). Furthermore, genetic alterations and phosphorylation of exportin 5 impair miRNA export from the nucleus and contribute to colorectal and liver cancer progression (67,68).

By contrast, altered expression of nuclear transport proteins is frequently observed in gynaecological tumours (Table I). Although nuclear transport proteins are typically overexpressed in tumour tissues, studies have shown that elevated levels can also be detected in the bloodstream of patients with cancer, even at early stages of disease (69,70). For example, van der Watt *et al* (70) identified KPNB1, XPO1, CAS, importin 5 and transportin 1 in the serum of patients with cervical and oesophageal cancers, with combinations of these proteins providing the greatest predictive value (70). Additional studies have shown that KPNB1 is overexpressed in cervical cancer tissue and contributes to tumour initiation and growth, supporting its potential as both a biomarker and therapeutic target (71,72). In ovarian cancer, elevated KPNB1 expression has been associated with poor prognosis (73). Importin 7 has also emerged as a promising diagnostic and prognostic biomarker in cervical cancer because of its high expression levels and association with disease progression (74). Other transport receptors, including karyopherin subunit α2 and XPO1, have been extensively investigated as diagnostic and prognostic markers in several malignancies, including ovarian cancer (42,75-80). Increased expression of circular RNA derived from transportin 3 has been reported in ovarian cancer and is associated with reduced sensitivity of ovarian cancer cells to paclitaxel (81). Elevated expression of CAS is associated with ovarian cancer progression (82). Notably, unlike several other transport receptors, karyopherin subunit α5 (KPNA5) has been proposed as a tumour suppressor, as reduced expression is associated with decreased overall survival in patients with ovarian cancer (83).

As summarised in Table I, ovarian cancer has been the most extensively investigated gynaecological malignancy in the context of nucleocytoplasmic transport, whereas comparatively limited data are available for cervical and endometrial cancers. Historically, ovarian cancer has attracted greater research attention because it has the highest mortality rate among gynaecological malignancies. Furthermore, numerous studies have demonstrated altered expression of nucleocytoplasmic transport factors in ovarian cancer, whereas relatively few transport-related molecular targets have been identified in cervical (70,72,74,84) and endometrial cancers (84-88). Consequently, the limited availability of validated molecular targets has further constrained research efforts in these malignancies.

4. Nuclear transport in relation to gynaecological cancer hallmarks

Alterations in nuclear transport play roles in tumorigenesis, and understanding their relationships with cell proliferation, survival and motility may improve the prediction of tumour aggressiveness and treatment resistance. Over the past decade, numerous studies across a range of malignancies, including gynaecological cancers, have investigated the contribution of nuclear transport machinery to the acquisition of cancer hallmarks.

In several cancer types, overexpression of XPO1 is associated with disease severity and adverse prognostic outcomes. In ovarian cancer, elevated XPO1 expression associates with tumour aggressiveness and reduced patient survival, whereas XPO1 inhibition exerts antiproliferative effects in cervical cancer cells *in vitro* (89). A study of chronic lymphocytic leukaemia identified several *XPO1* mutations that appear to confer selective advantages for cellular proliferation and survival and may predispose cells to leukemic transformation in the presence of additional genetic alterations; however, further investigation is required to validate these findings (90). In ovarian cancer, XPO1 expression has been shown to be significantly associated with epidermal growth factor receptor (EGFR), a key regulator of cellular growth. Moreover, XPO1 inhibition reduced EGFR protein levels, suggesting this interaction may contribute to tumour progression and cancer cell proliferation (91).

Furthermore, increased XPO1 activity promotes export of tumour suppressor proteins, including p27 and p53, from the nucleus to the cytoplasm, inactivating them by sequestering them from their primary sites of action. Cytoplasmic localisation of p27 and p53 has been associated with poor prognosis and therapeutic resistance in several malignancies, including gynaecological cancers. For example, XPO1 recognises p27 phosphorylated at serine 10 (pSer10-p27) and exports it to the cytoplasm, where it acquires oncogenic properties. In epithelial ovarian cancer, XPO1 and pSer10-p27 expression levels are positively associated, and elevated expression of both proteins is associated with reduced overall survival, higher International Federation of Gynaecology and Obstetrics stage and increased tumour grade. The same study demonstrated that XPO1 knockdown inhibited the nuclear export of pSer10-p27 and reduced ovarian cancer cell proliferation *in vitro* (92). An investigation of serous ovarian carcinoma revealed that cytoplasmic p53 forms aggregates that are associated with poor prognosis and reduced sensitivity to cisplatin, suggesting a potential role in chemotherapy resistance, although the study did not specifically investigate XPO1-mediated p53 transport (93). Moreover, leptomycin B inhibition of XPO1 sensitised chemoresistant endometrial and ovarian cancer cells to TRAIL-induced apoptosis through a p53-independent mechanism. Clonogenic assays further showed that combination treatment of TRAIL and leptomycin B notably reduced long-term colony-forming capacity, indicating that XPO1 may contribute to sustained tumour growth and proliferative potential (94).

Table I. Changes in nuclear transport protein expression in gynaecological tumours and their relevance to disease progression.

Type of cancer	Protein	Change in expression	Effect	(Refs.)
Ovarian	XPO1	Increased	Associated with poor patient prognosis and expression of COX-2	(78)
Ovarian	XPO1	Increased	Associated with poor patient prognosis and resistance to platinum-based therapy	(77)
Ovarian	KPNA2	Increased	Elevated migration and invasion of epithelial ovarian cancer cells, knockdown of KPNA2 suppressed epithelial-to-mesenchymal transition characteristics	(79)
Ovarian	KPNA2	Increased	Associated with poor patient prognosis	(80)
Ovarian	KPNA2	Increased concentration in blood samples	Proposed as a diagnostic marker	(76)
Ovarian	KPNA5	Decreased	Associated with poor patient prognosis, overexpression decreased tumour growth and invasion	(83)
Ovarian	KPNB1	Increased	Associated with poor patient prognosis, inhibition decreased ovarian cancer cell proliferation, invasion and induced apoptosis	(73,121)
Ovarian	TNPO3	Increased (circular RNA)	Mediates paclitaxel resistance of ovarian cancer cells	(81)
Ovarian	CAS	Increased	Associated with disease progression	(82)
Cervical	XPO1, KPNB1 and KPNA2	Increased	Inhibition of XPO1 and KPNB1 decreased cervical cancer cell proliferation and induced apoptosis	(72)
Cervical	KPNB1, XPO1, CAS, IPO5 and TNPO1	Increased concentration in blood samples	Proposed as diagnostic markers	(70)
Cervical	IPO7	Increased	Associated with poor patient prognosis, knockdown decreased cervical cancer cell proliferation	(74)
Cervical	NUTF2	Increased	Associated with the number of infiltrating cancer-associated fibroblasts	(84)
Endometrial	XPO1	Increased	Associated with poor patient prognosis	(85)
Endometrial	KPNA2	Increased	Proposed as a prognostic marker for poor patient survival. Gene silencing slowed down endometrial cancer cell proliferation rate	(86)
Endometrial	IPO13	Increased	Proposed as a progenitor/stem cell marker	(87)
Endometrial	NXF1	Decreased	Inhibited endometrial cancer progression *in vitro* and *in vivo*	(88)
Endometrial	NUTF2	Increased	Increased expression in comparison to healthy tissue was associated with an oncogenic role	(84)

XPO1, exportin 1; KPNA2, karyopherin subunit α2; KPNA5, karyopherin subunit α5; KPNB1, karyopherin subunit β1; TNPO3, transportin 3; IPO5, importin 5; IPO7, importin 7; NUTF2, nuclear transport factor 2; IPO13, importin 13; NXF1, nuclear RNA export factor 1.

Among other exportins, Li *et al* (95) reported that reduced XPO5 stability, together with required for meiotic nuclear division 5 homolog A protein downregulation, inhibited migration of HeLa cervical cancer cells, highlighting a possible role for XPO5 in tumour cell motility.

In contrast to the elevated expression of XPO1, KPNA5 is frequently downregulated in ovarian cancer and is associated with poor patient outcomes, whereas maintained or elevated KPNA5 expression suppresses tumour growth. KPNA5 mediates the nuclear import of the phosphatase protein tyrosine phosphatase non-receptor type 4 (PTPN4), which dephosphorylates STAT3 and inhibits its activation (83). STAT3 is a transcription factor that promotes tumour cell growth and survival while suppressing antitumour immune responses (96). A study by Hu *et al* (83) confirmed that KPNA5 interacts with PTPN4 and facilitates its transport from the cytoplasm to the nucleus in the ovarian cancer cell lines SKOV3 and OVCAR3. The authors further demonstrated that KPNA5 overexpression inhibited ovarian cancer cell migration and invasion *in vitro* (83).

Li *et al* (84) also analysed 33 cancer types to investigate the oncogenic role of nuclear transport factor 2 (NUTF2), a GDP-binding protein involved in nucleocytoplasmic transport. Compared with that in adjacent normal tissues, NUTF2 expression was elevated in 19 cancer types, including cervical and endometrial carcinomas. To further explore its

biological role, the authors performed gene co-expression analyses. NUTF2 expression was positively associated with the proliferation markers proliferating cell nuclear antigen and marker of proliferation KI-67 in 16 tumour types. In addition, expression of the epithelial-to-mesenchymal transition markers vimentin, *TWIST1*, *SNAI1*, *SNAI2*, fibronectin 1 and N-cadherin were positively associated with NUTF2 expression across most tumour types. These findings suggest that NUTF2 may contribute to both cancer cell proliferation and metastatic dissemination by regulating cellular motility.

Fig. 2 summarizes alterations in nuclear transport proteins in gynaecological cancers and their associations with specific cancer hallmarks.

5. Targeting nuclear transport to treat gynaecological cancer

Discoveries of dysregulated nucleocytoplasmic transport in gynaecological tumours have highlighted its therapeutic potential. Nucleocytoplasmic transport inhibitors fall into two broad categories: Nuclear import inhibitors and nuclear export inhibitors (97,98).

Nuclear export inhibition. XPO1 is a ubiquitously expressed protein in eukaryotic cells. First identified in yeast, it has since been shown to mediate the nuclear export of hundreds of proteins (99). Studies of the natural compound leptomycin B (LMB), an inhibitor of XPO1, facilitated the identification of XPO1 cargo proteins. Among all exportins, XPO1 uniquely exports a broad spectrum of biologically important proteins, including tumour suppressors and growth regulators such as p53, p21 and FOXO, as well as key signalling molecules involved in the PI3K/AKT, Wnt/β-catenin, activator protein-1 and NF-κB pathways (100). Mechanistically, XPO1 inhibitors promote the nuclear retention of tumour suppressor proteins, thereby restoring their function. Even when a specific tumour suppressor, such as p53, is mutated or inactive, the abnormal accumulation of multiple tumour suppressors and growth-inhibitory factors within the nucleus can overwhelm cellular defence mechanisms and trigger programmed cell death (101). This class of inhibitors targets the cysteine residue Cys528 within the NES-binding groove of XPO1, preventing nuclear export of regulatory molecules and suppressing cell proliferation (100,102).

Research on nuclear export inhibitors began with LMB, a naturally occurring antifungal compound and the first identified XPO1 inhibitor (100). Similar to several subsequently developed compounds, LMB binds covalently to the Cys528 residue; however, its clinical development was discontinued because of severe dose-limiting gastrointestinal toxicity (89). Other naturally occurring XPO1 inhibitors include ratjadone C, anguinomycin and goniothalamin (100). Curcumin has also been reported to inhibit XPO1 by covalently binding to Cys528, resulting in nuclear accumulation of cargo proteins such as forkhead box protein O1 (FOXO1) (103). Although curcumin suppresses cell proliferation, its efficacy appears to be lower than that of synthetic XPO1 inhibitors (104).

The limitations of LMB prompted the development of synthetic compounds with improved safety profiles, most notably the selective inhibitors of nuclear export (SINEs). This group includes Selinexor (KPT-330), Verdinexor (KPT-335), KPT-185, KPT-251 and KPT-276. Similar to LMB, these compounds target the Cys528 residue of XPO1, but their interaction is reversible (Fig. 3A and B) (100). This reversibility reduces toxicity while maintaining anticancer activity. Selinexor is the most clinically advanced SINE and has been evaluated in >40 clinical trials across over 10 cancer types, including gynaecological malignancies (105). These studies ultimately led to approval by the Food and Drug Administration (FDA) for penta-refractory multiple myeloma (102). Verdinexor has also been investigated for treating viral infections, particularly influenza (106). Although compounds such as KPT-185 have demonstrated promising activity *in vitro*, their clinical development has been limited by unfavourable pharmacokinetic properties (107).

CBS9106, also known as felezonexor or SL-801, represents a distinct class of synthetic XPO1 inhibitors with dual mechanisms of action. In addition to reversibly inhibiting XPO1 and inducing apoptosis, this orally bioavailable compound markedly reduces XPO1 protein levels without affecting corresponding mRNA expression (108). XPO1 degradation occurs through the Cullin-RING ligase system and the neddylation pathway. Understanding this mechanism matters because it suggests that CBS9106 may show antagonistic interactions when combined with neddylation inhibitors or proteasome inhibitors (109). At present, no studies have specifically evaluated CBS9106 in gynaecological cancers. The CBS9106 derivative S109 is currently under development because it is simpler and more cost-effective to synthesize, facilitating large-scale production (110).

Nuclear import inhibition. The preclinical and clinical success of XPO1-targeted therapies has stimulated the development of nuclear import inhibitors. Although this field remains at an early stage, targeting importins has shown considerable promise, with several small-molecule inhibitors already demonstrating anticancer activity in preclinical studies. In contrast to XPO1 inhibitors, which uniformly target the well-characterised NES-binding pocket, the binding sites and mechanisms of action of several nuclear import inhibitors remain incompletely understood.

Nuclear import inhibitors can be broadly classified into two groups: Direct importin inhibitors, which target the transport receptor itself, and cargo-specific inhibitors, which prevent the import machinery from recognizing individual cargo proteins (102). Direct importin inhibitors aim to disrupt the core nuclear transport apparatus. For example, the FDA-approved antiparasitic drug ivermectin binds the importin α/β1 heterodimer and blocks the nuclear import of viral proteins, including HIV-1 integrase, dengue virus NS5 and influenza virus proteins, thereby exerting broad-spectrum antiviral activity. However, this mechanism also affects host signalling pathways, including the HIF-1α pathway (73,111). The pleiotropic effects of importin inhibition are particularly relevant in cancer, as numerous oncogenic transcription factors and signalling mediators depend on importin-mediated nuclear translocation to exert their tumour-promoting functions.

In cancer cells, ivermectin binds importin β1 and inhibits nuclear transport (Fig. 3C and D). This prevents activated ERK5

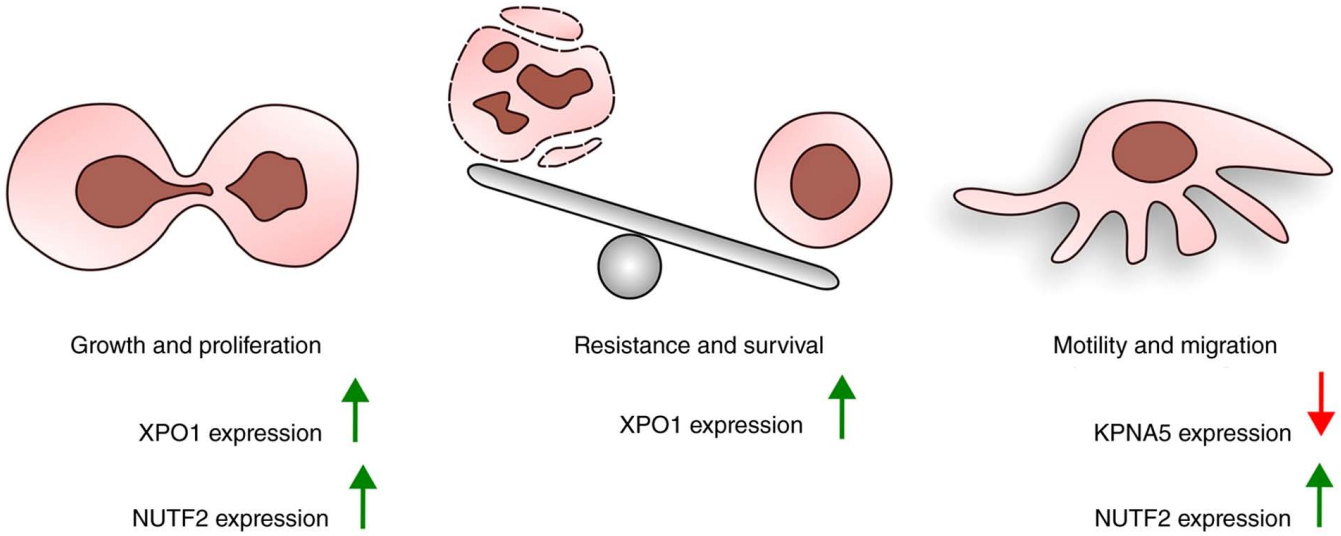

Figure 2. Cancer hallmarks and associated gene expression alterations in gynaecological tumours. Increased XPO1 and NUTF2 expression is associated with enhanced cell growth and proliferation, whereas elevated XPO1 expression is associated with cell resistance and survival. Reduced KPNA5 and increased NUTF2 expression are associated with increased motility and migration. XPO1, exportin 1; NUTF2, nuclear transport factor 2; KPNA5, karyopherin subunit α5.

from entering the nucleus, retaining it in the cytoplasm and inhibiting its pro-proliferative activity (112). Given the recognised role of ERK5 signalling in cell proliferation, survival and therapeutic resistance, including in gynaecological malignancies, these findings provide a mechanistic basis for targeting nuclear import pathways in cancer treatment (113,114). Similarly, the synthetic compound importazole directly targets importin β1 and impairs cargo transport by disrupting its interaction with RanGTP (115-117). This mechanism was first demonstrated for the importin β1 inhibitor karyostatin 1A, described in 2010, which prevents dissociation of the importin β1/importin α/cargo complex within the nucleus and thereby blocks classical nuclear import (118). Dissociation of this complex is essential for successful transport because it ensures cargo release within the nucleus rather than its return to the cytoplasm alongside the transport receptor. More recently, synthetic compounds such as INI-43 and INI-60, identified through *in silico* screening approaches (119), have further demonstrated the therapeutic potential of this strategy. INI-43 inhibits cancer cell growth and induces G2/M cell-cycle arrest by preventing nuclear import of pro-survival proteins, including NF-κB (120,121).

Aberrant activation of NF-κB has been extensively documented in ovarian cancer, where it contributes to chemoresistance, stemness, metastatic progression and survival signalling (122). Dysregulated NF-κB signalling has also been implicated in endometrial carcinoma and other endometrial disorders, linking this pathway to multiple gynaecological malignancies (123). Nevertheless, caution is warranted when extrapolating these findings to gynaecological cancers. Although dysregulation of NF-κB and ERK5 signalling is a recognised feature of gynaecological tumour biology, most mechanistic and efficacy studies involving ivermectin, importazole, INI-43 and INI-60 have been performed in non-gynaecological malignancies, including glioblastoma, oesophageal cancer and haematological cancers (120,124-127), or in preliminary cell-line models (120). Direct validation in disease-specific gynaecological models, particularly primary ovarian and endometrial tumours, patient-derived xenografts and clinical studies, remains lacking and represents an important area for future research.

In contrast to broadly acting importin inhibitors, cargo-specific inhibitors offer a more selective therapeutic approach by binding directly to the NLS of a specific cargo protein. This prevents cargo recognition by the import machinery and may reduce off-target toxicity (Fig. 4A and B). Examples include the corticosteroids budesonide and flunisolide, which bind the NLS of HIV-1 integrase and block its importin α/β1-mediated nuclear import. Mifepristone exerts a similar effect on HIV-1 integrase, although its clinical development was discontinued (128,129). Another example is the retinoid 4-HPR (fenretinide), which selectively disrupts the NS5/importin α/importin β1 interaction in flaviviruses, thereby inhibiting dengue and Zika virus infection without disturbing essential host nuclear import pathways (130). Although most cargo-specific inhibitors have been developed in antiviral settings, their mechanism of action is attractive for cancer therapy because it enables selective inhibition of oncogenic nuclear signalling while potentially minimising systemic toxicity.

An increasing number of studies have explored cargo-specific nuclear import inhibitors in cancer treatment (131-133). Collectively, current evidence suggests that although direct importin inhibitors provide potent, broad-spectrum activity, cargo-specific approaches may offer greater selectivity and reduced toxicity (102). Taken together, these findings support nuclear import inhibition as a mechanistically rational, albeit largely preclinical, therapeutic strategy that merits further investigation alongside the more clinically advanced nuclear export inhibitors.

However, the literature on cargo-specific nuclear import inhibitors in gynaecological cancers remains limited. Although this approach offers potential to avoid the toxicities associated with global inhibition of nucleocytoplasmic

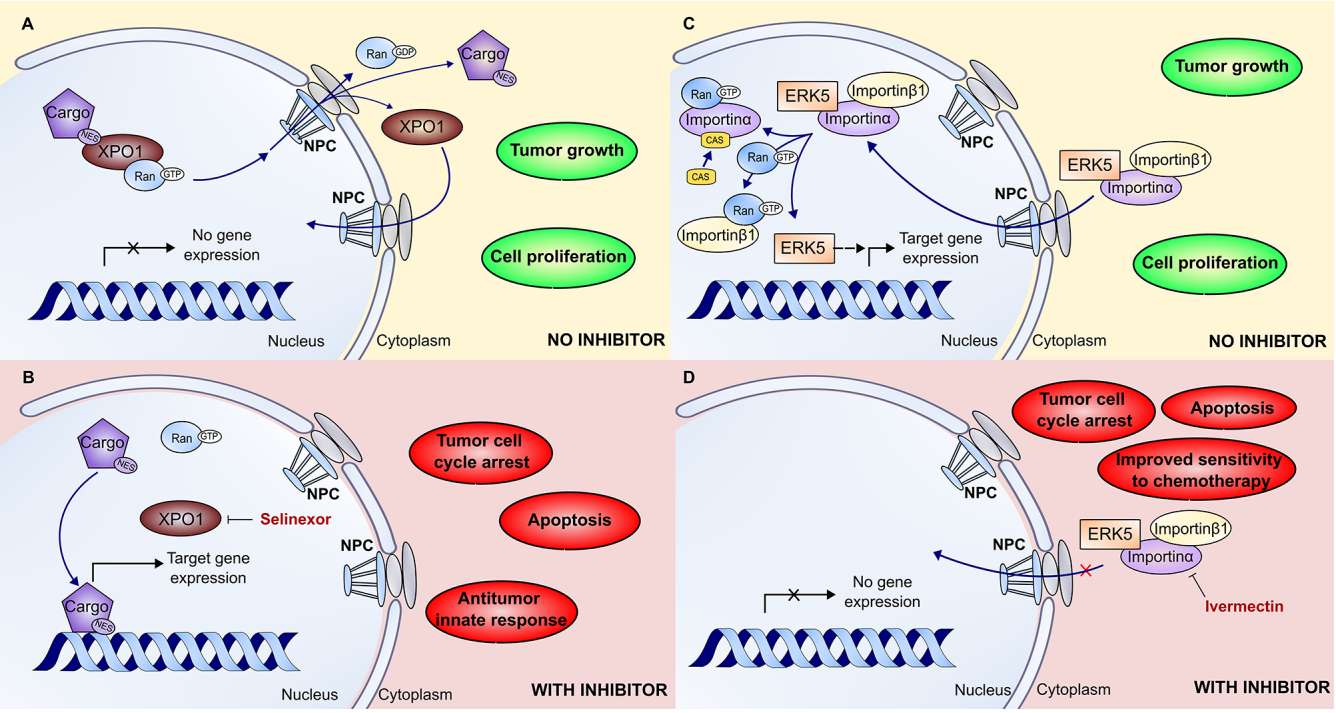

Figure 3. Mechanisms of action of nuclear transport inhibitors in tumour cells. (A) The mechanism of nuclear export mediated by XPO1 and the inhibitory effects of Selinexor in tumour cells. In cancer cells, XPO1 binds nuclear cargo proteins carrying an NES, along with RanGTP, and transports them through the NPC into the cytoplasm. After dissociation of the complex, RanGTP is hydrolysed to RanGDP, and XPO1 is transported back into the nucleus to sustain the export cycle. The continuous nuclear export of tumour suppressor proteins disables their nuclear function and gene expression, thereby supporting tumour cell proliferation and tumour growth. (B) With XPO1 inhibition by Selinexor, the interaction between XPO1 and NES-containing cargo proteins is blocked, leading to their nuclear retention and restoration of transcriptional activity. This leads to tumour cell cycle arrest, apoptosis and an antitumor innate response. (C) In cancer cells, ERK5 binds to the importinα/β1 complex, enabling its nuclear import through the NPC. Once inside the nucleus, the import complex dissociates: ERK5 is released and functions as a transcriptional regulator, promoting target gene expression that drives tumour cell proliferation and tumour growth, whereas importinα and importinβ1 dissociate, bind RanGTP and return to the import cycle. (D) When ERK5 nuclear import is inhibited by ivermectin, the interaction between ERK5 and the importin transport machinery is blocked, preventing ERK5 from entering the nucleus. Consequently, ERK5-mediated transcriptional activity is suppressed, resulting in tumour cell cycle arrest, apoptosis and improved sensitivity to chemotherapy. NES, nuclear export signal; NPC, nuclear pore complex; XPO1, exportin 1.

transport, most validated cargo-specific inhibitors, including budesonide, flunisolide and fenretinide, currently target viral proteins rather than oncogenic drivers relevant to ovarian, cervical or endometrial cancers (124). Future research should therefore focus on identifying critical nuclear localisation sequences within key gynaecological oncogenes to facilitate the development of tumour-specific nuclear import inhibitors and address this important translational gap.

Preclinical studies of nuclear export and import inhibitors. In gynaecological cancers, particularly endometrial and ovarian cancers, several compounds targeting nuclear transport pathways have shown notable anticancer effects. Among nuclear export inhibitors, Selinexor has shown clinically meaningful activity in endometrial cancer. In the phase III SIENDO trial, a prespecified subgroup analysis demonstrated that Selinexor significantly prolonged progression-free survival (PFS) in patients with *TP53* wild-type tumours, with a median PFS of 28.4 months compared with 5.2 months for placebo [hazard ratio 0.44; 95%; confidence interval (CI), 0.27-0.73; nominal P=0.0005]. These results support Selinexor as a biomarker-driven therapeutic strategy beyond its current FDA approval in hematologic malignancies. However, the authors note two main limitations of the SIENDO trial: A low number of patients with TP53-wt (113) and that certain patients (in both the Selinexor and placebo groups) discontinued before completing treatment. Given the fact that analysis was prespecified and the primary endpoint in the intent-to-treat population was not met, the subgroup analysis is exploratory, and the results are not conclusive. Additionally, >94% of patients were white and had endometrioid carcinoma; thus, the results do not reflect diverse populations and rare subtypes of endometrial cancer. As the study evaluated Selinexor in pretreated patients who previously received chemotherapy, the efficacy of Selinexor in untreated patients remains unknown. The SIENDO trial motivated the subsequent XPORT-EC-042 trial [NCT05611931, registered (first posted) at ClinicalTrials.gov 2022-11-10] (134). Although this study also focuses on pretreated patients with *TP53*-wt, the group size is approximately twice as large (276 participants), and the distribution between treatment arms is more balanced (1:1 Selinexor vs. placebo compared with 2:1 in the SIENDO trial). Selinexor also demonstrated activity in heavily pretreated ovarian and endometrial cancers. In an open-label, single-arm phase II study, median PFS was 2.6 months in ovarian cancer and 2.8 months in endometrial cancer patients treated with Selinexor (135). Similar to the SIENDO trial, this study also included previously pretreated patients; the groups differed in size and were relatively small

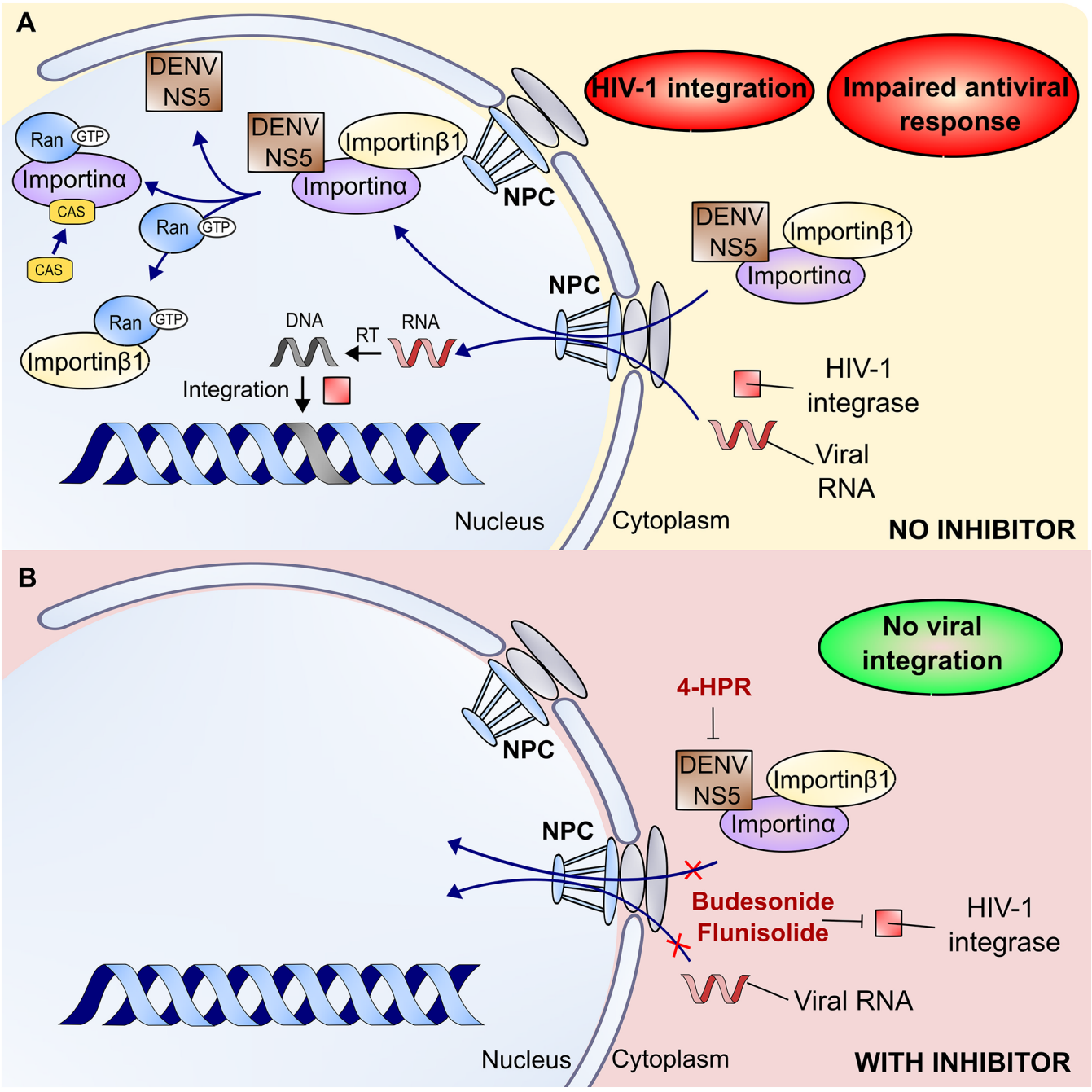

Figure 4. Mechanisms of action of nuclear transport inhibitors in virus-infected host cells. (A) Infected host cells use the importinα/β1 complex to recognize and transport the viral proteins DENV NS5 and HIV-1 integrase through the NPC into the nucleus. Once inside the nucleus, the importinα/β1 complex dissociates, releasing viral proteins to interfere with host cellular functions-DENV NS5 by disrupting antiviral responses and integrase by integrating viral DNA, which is reverse transcribed from the viral RNA, into the host genome. (B) Cargo-specific inhibitors work by binding directly to the viral cargo; 4-HPR binds to DENV NS5, whereas budesonide and flunisolide bind to the HIV-1 integrase. Direct binding prevents viral proteins from being recognized by the host's importinα/β1 complex, thereby effectively blocking their nuclear import and leading to a lack of viral integration. 4-HPR, N-(4-hydroxyphenyl) retinamide; NPC, nuclear pore complex; RT, reverse transcriptase; DENV, dengue virus.

(66 patients with ovarian cancer, 23 patients with endometrial cancer and 25 patients with cervical cancer). The authors assessed treatment response in 98 of 114 patients, and the absence of a placebo group limits direct comparison with other clinical trials. Although the authors performed circulating tumour cell analysis to assess treatment outcome, the subset of patients was small (31 patients with ovarian cancer, 8 patients with endometrial cancer and 6 patients with cervical cancer), so the findings are preliminary. The modest PFS and their differences in ovarian, endometrial and cervical cancer could be explained by a small sample size and different numbers of patients with highly resistant platinum-refractory tumours in the groups. The authors also note that Selinexor may yield better outcomes in combination with other treatment modalities (radiation therapy, targeted therapy or immunotherapy), especially because combination results in preclinical models (cell lines and mice) are promising (136-138). Identifying biomarkers to predict sensitivity to Selinexor in patients

with gynaecological cancer could also improve outcomes. In platinum-resistant ovarian cancer models, XPO1 inhibition restored platinum sensitivity and induced apoptosis independently of p53 status (77). By contrast, among nuclear import inhibitors, ivermectin and the structurally related compounds INI-60 and INI-43 have shown anticancer activity by inhibiting importin β1, with selective cytotoxicity observed in cervical cancers (73,120,121). Ivermectin alone inhibited ovarian cancer growth by inducing cell cycle arrest and caspase-dependent apoptosis (139). Additionally, ivermectin showed importin β1-dependent antitumor activity in epithelial ovarian cancer, highlighting its potential for drug repurposing in this setting (73). Other compounds with anticancer effects in gynaecological cancers include budesonide, which has demonstrated antitumor activity in ovarian cancer cells (140), and fenretinide, which reduces viability and induces apoptosis in endometrial cancer Ishikawa cells in a dose-dependent manner (131). Notably, the effects of fenretinide were independent of retinoic acid receptor signalling and appeared to be mediated by increased retinol uptake via stimulated by retinoic acid 6 (STRA6), as silencing STRA6 notably reduced apoptosis. *In vivo*, intraperitoneal fenretinide treatment effectively suppressed tumour growth in mice bearing Ishikawa-derived endometrial tumours (131).

Combination therapies that include nuclear transport inhibitors. Conventional chemotherapies disrupt fundamental cellular processes, such as DNA replication and cell proliferation. However, they cannot distinguish between malignant and healthy cells, often resulting in substantial toxicity. By contrast, targeted therapies selectively inhibit cancer-associated pathways that normal cells depend on less. Nevertheless, dose-limiting toxicities and the emergence of drug resistance can compromise therapeutic efficacy. Consequently, combination therapy is frequently favoured over monotherapy. By concurrently targeting multiple oncogenic pathways, combination regimens may overcome resistance mechanisms that limit the effectiveness of both conventional and emerging anticancer agents (141). Furthermore, identifying synergistic or additive drug interactions may allow dose reduction without compromising therapeutic efficacy, thereby decreasing the frequency and severity of adverse effects (142).

Among gynaecological malignancies, particularly ovarian and cervical cancers, this strategy has shown considerable promise. Regarding nuclear import inhibition, ivermectin has shown importin β1-dependent antitumour activity in epithelial ovarian cancer, suppressing proliferation and inducing apoptosis by increasing expression of p21, p27 and Bax (73). Ivermectin also exhibited synergistic activity with paclitaxel in chemoresistant epithelial ovarian cancer models (143), while nanoparticle-based formulations have been investigated in combination with pitavastatin to improve therapeutic outcomes in ovarian cancer (144). In addition, ivermectin notably enhanced cisplatin efficacy in a dose-dependent manner. In xenograft mouse models, ivermectin monotherapy suppressed tumour growth, whereas combination treatment with cisplatin completely reversed tumour progression without observable toxicity at pharmacologically relevant concentrations (139). In cervical cancer, the nuclear import inhibitor INI-43 showed synergistic cytotoxicity with cisplatin by activating the p53 and NF-κB signalling pathways, highlighting its potential to improve outcomes in cisplatin-resistant disease and reduce treatment-related toxicity through dose reduction (145).

Conversely, selinexor, a nuclear export inhibitor, has demonstrated encouraging clinical activity in combination with weekly paclitaxel in ovarian cancer, with manageable toxicity and support for further evaluation in randomised trials. In the intention-to-treat population, the combination achieved a median PFS of 6.7 months (95% CI, 3.3-10.7 months) (146). Moreover, selinexor showed synergistic activity when combined with the PARP inhibitor olaparib, reducing DNA repair protein expression, increasing tumour suppressor expression and enhancing tumour cell death in ovarian cancer models (138).

6. Mechanisms of resistance to nuclear transport inhibitors

Despite the novel mechanism of action and initial clinical success in the treatment of refractory haematological and solid tumours, the efficacy of SINE compounds is ultimately limited by the development of resistance (Fig. 5). A comprehensive understanding of these resistance mechanisms is essential for the rational development of combination therapies, optimisation of current clinical applications and design of next-generation nuclear transport inhibitors. In gynaecological cancers, resistance to SINE compounds may arise from *XPO1* mutations that prevent inhibitor binding. Furthermore, evidence suggests an association between *TP53* mutation status and resistance to Selinexor in endometrial cancer cells. Other resistance mechanisms, including global transcriptional reprogramming observed in multiple myeloma and cytoprotective autophagic responses reported in glioblastoma, represent broader mechanistic frameworks that are not specific to gynaecological malignancies. Additionally, SINE compounds have shown potential to sensitise tumour cells to other anticancer therapies and overcome existing treatment resistance.

Mechanisms of SINE resistance in gynaecological cancers. The principal genetic resistance mechanism identified across multiple preclinical models involves substitution of XPO1 cysteine 528 with serine (C528S) (147). This single amino acid substitution eliminates the reactive thiol group of Cys528, rendering the binding pocket chemically inert to the covalent interaction required for SINE-mediated inhibition (148). Cells engineered to express the *XPO1*-C528S mutant display complete resistance to Selinexor, as demonstrated by the continued cytoplasmic localisation of critical XPO1 cargo proteins, such as RanBP1, following treatment. These findings indicate that the C528S mutation is sufficient to preserve the oncogenic nuclear export activity required for cellular survival despite drug exposure (149).

Notably, this resistance mechanism behaves dominantly. Experimental modelling using CRISPR/Cas9 genome editing demonstrated that a heterozygous C528S mutation confers a resistance phenotype comparable to that observed in homozygous mutant cells (150). In heterozygous cells, although the wild-type *XPO1* allele remains susceptible to Selinexor inhibition, the mutant allele continues to produce fully functional XPO1 protein capable of exporting tumour suppressor proteins (TSPs) from the nucleus. This residual export activity

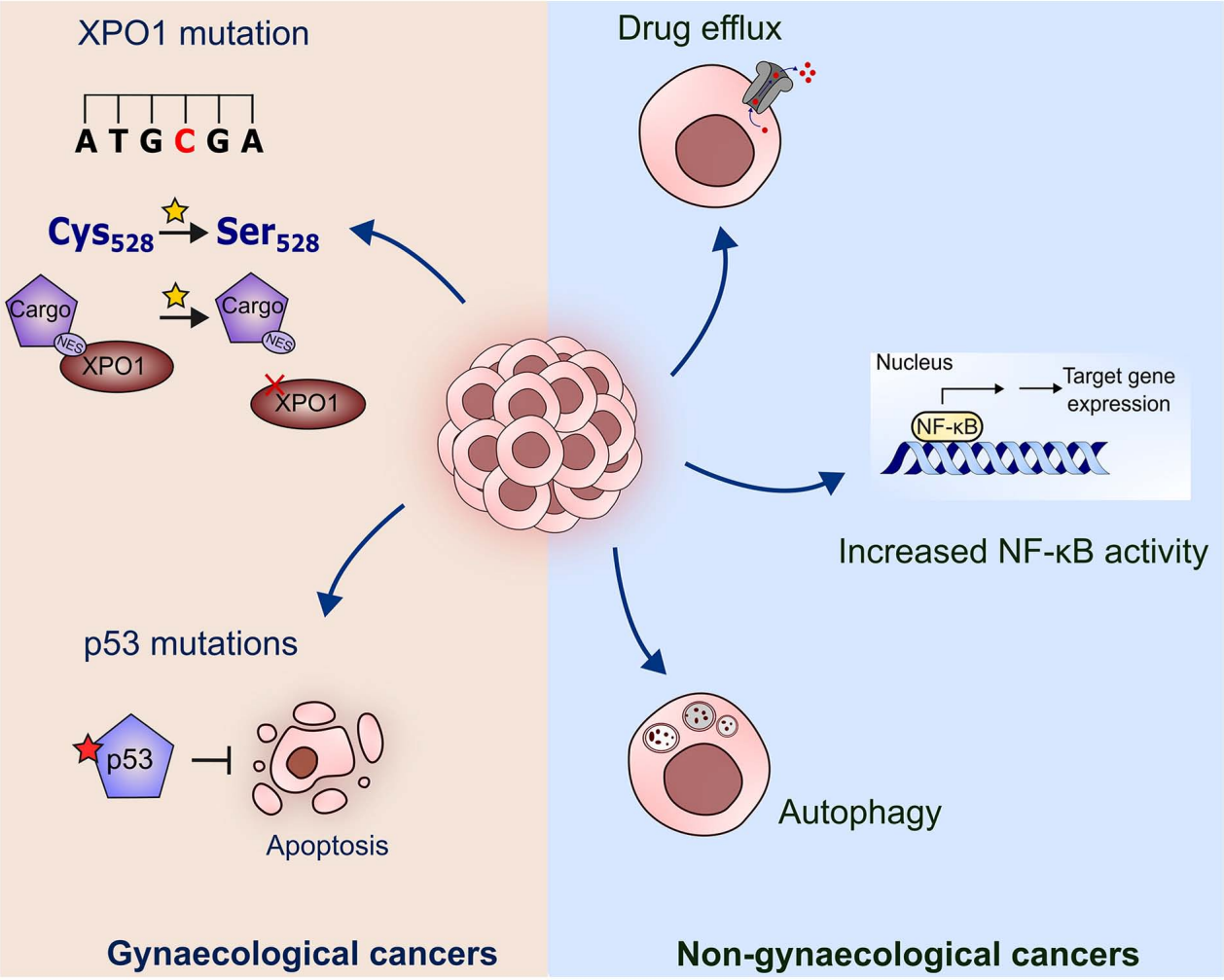

Figure 5. Mechanisms of resistance to nuclear transport inhibitors. Resistance to selective inhibitors of nuclear export compounds, such as Selinexor, arises through diverse and interconnected mechanisms spanning genetic, pharmacokinetic, and pharmacodynamic challenges. Left side illustrates mechanisms in gynaecological cancers: a critical genetic escape mechanism is the dominant XPO1 cysteine 528 to serine mutation, which abolishes the necessary covalent drug binding, leaving the protein active to export tumour suppressor proteins; p53 mutations determine the loss of its ability to induce apoptosis, allowing cancer cells to survive despite cellular stress or damage. Right side overviews mechanisms in non-gynaecological cancers: pharmacokinetic resistance often involves the overexpression of efflux pumps, which actively expel the drug, reducing its intracellular concentration below therapeutic levels; pharmacodynamic resistance manifests as cellular reprogramming, including the activation of compensatory prosurvival pathways, such as the NF-κB pathway, to bypass the nuclear retention of tumour suppressor proteins, and the induction of cytoprotective autophagy. NES, nuclear export signal; XPO1, exportin 1.

is sufficient to maintain essential nucleocytoplasmic transport processes and to keep nuclear TSP concentrations, including RanBP1, below the threshold required to induce effective apoptosis. Consequently, a single mutational event may be sufficient to negate the therapeutic activity of SINE compounds, representing an efficient escape mechanism for cancer cells. Furthermore, because both first-generation (Selinexor) and second-generation (KPT-8602) SINE compounds depend on covalent binding to Cys528, this mutation confers cross-resistance to both classes of inhibitors (151).

The *XPO1*-C528S mutation has also been implicated in resistance to the novel XPO1 inhibitor S109 in ovarian cancer cells. In cells expressing the mutant protein, S109 failed to induce significant nuclear accumulation of the tumour suppressor proteins Foxo1 and p27, a key component of its mechanism of action. Moreover, *XPO1*-C528S-expressing cells resisted the growth-inhibitory effects of S109 at the tested concentrations, whereas cells expressing wild-type *XPO1* showed significant growth suppression (152). However, no published clinical studies have established a role for the *XPO1*-C528S mutation as a mechanism of resistance to XPO1 inhibitors in patients with gynaecological cancers. Thus, the significance of this mutation remains primarily mechanistic rather than clinical, serving as a model of target-mediated resistance rather than an established acquired biomarker.

Not all *XPO1* mutations confer resistance to SINE compounds. Clinical genomic profiling has identified alternative *XPO1* alterations in gynaecological malignancies. Among these, the *XPO1*-R749Q mutation is a recurrent variant enriched in endometrial cancer, accounting for ~50% of reported R749Q cases in solid tumours and frequently co-occurring with polymerase epsilon hotspot mutations. This variant is particularly prevalent in tumours with high tumour mutational burden and may confer resistance to conventional topoisomerase I inhibitors while retaining sensitivity to Selinexor-based combination therapies (153).

In addition to *XPO1* alterations, resistance to SINE compounds in gynaecological malignancies may be influenced

by tissue-specific molecular characteristics, particularly the high prevalence of *TP53* mutations. Results from the Phase III SIENDO trial demonstrated that the efficacy of Selinexor maintenance therapy in advanced or recurrent endometrial cancer is strongly dependent on molecular subtype. Patients with *TP53* wild-type tumours experienced substantially prolonged median PFS, whereas those with *TP53*-mutant tumours derived no notable benefit from treatment (154,155). Mechanistically, Selinexor promotes nuclear accumulation of wild-type p53 and restores its tumour-suppressive functions, leading to cell-cycle arrest and apoptosis. By contrast, tumours harbouring dysfunctional mutant p53 are less likely to benefit from this therapeutic mechanism (156).

Several agents that restore p53 function are currently under clinical investigation and may enhance the efficacy of Selinexor. APR-246, a small-molecule p53 reactivator, is undergoing clinical evaluation for high-grade serous ovarian carcinoma and has shown particularly promising activity in tumours with low CIP2A expression (157). APR-246 has also been reported to restore sensitivity to DNA-damaging agents in both established and primary ovarian cancer cells with acquired drug resistance (158). Another p53-reactivating agent, COTI-2, successfully completed a Phase I trial in recurrent gynaecological cancers (NCT02433626; first registered on ClinicalTrials.gov on 5 May 2015) and has received FDA orphan drug designation for ovarian cancer treatment (159). A total of ~3% of ovarian tumours harbour the TP53 Y220C mutation, for which the mutant p53-targeting agent PC14586 has demonstrated encouraging clinical activity (160).

Despite their potential, none of these p53-restoring compounds have yet been evaluated in combination with nuclear export inhibitors. To date, only combinations of Selinexor and PARP inhibitors have demonstrated preclinical efficacy, although not specifically in TP53-mutant gynaecological cancers. These studies focused primarily on therapeutic synergism rather than mechanisms of Selinexor resistance. In ovarian cancer, screening of 688 compounds identified the PARP inhibitor Olaparib as the most synergistic partner for Selinexor, a finding subsequently validated in both cell-line and mouse models. Combination treatment reduced DNA repair protein expression while increasing tumour suppressor protein levels. However, these experiments used the A2780 cell line, which carries wild-type *TP53*; therefore, the observed synergy cannot be attributed to restoration of mutant p53 function (138).

The synergistic interaction between Selinexor and Olaparib was also confirmed in the OVCAR5 mouse model; however, the TP53 status of OVCAR5 cells remains controversial, with conflicting reports describing the cell line as either wild-type or functionally deficient. Notably, the Selinexor-Olaparib combination was effective in the *TP53*-mutant breast cancer cell lines MDA-MB-468 and MDA-MB-436, inducing cell-cycle arrest and cell death *in vitro* and suppressing tumour growth in xenograft models *in vivo* (161). Although that study did not focus on *TP53* mutation status, these findings provide preclinical evidence supporting the potential utility of Selinexor-based combination therapies in *TP53*-mutant cancers.

Mechanisms of SINE resistance in non-gynaecological cancers. Beyond structural alterations in the XPO1 target protein, resistance mechanisms involving drug efflux and global cellular adaptation also play important roles in limiting the efficacy of SINE compounds in several tumour types.

Multidrug resistance (MDR) is frequently associated with overexpression of ATP-binding cassette (ABC) transporters, including P-glycoprotein (P-gp/ABCB1), multidrug resistance-associated proteins (MRPs) and breast cancer resistance protein (BCRP). These membrane-bound transporters function as active efflux pumps, utilising ATP hydrolysis to export a broad range of structurally diverse substrates, including several hydrophobic small-molecule chemotherapeutic agents, from the cell (162). In gynaecological malignancies, including cervical and ovarian cancer, MDR is commonly mediated by overexpression of drug efflux pumps, particularly P-gp and MRP1, which reduce intracellular drug accumulation and consequently diminish therapeutic efficacy (163-165).

As SINE compounds are small, hydrophobic molecules, they are recognised and transported by ABC efflux pumps (166). Overexpression of P-gp, often resulting from gene amplification or transcriptional and epigenetic alterations, markedly reduces intracellular drug accumulation and lowers intracellular SINE concentrations (162). This pharmacokinetic mechanism provides an alternative route to resistance that does not require genetic alteration of the XPO1 target. Consequently, treatment failure may occur despite retention of wild-type *XPO1*, owing to inadequate intracellular drug concentrations rather than loss of target sensitivity. In addition, ABC transporters substantially influence the systemic pharmacokinetics of SINE compounds by affecting their absorption, distribution and excretion, while also limiting penetration into pharmacological sanctuary sites such as the brain and cerebrospinal fluid (167).

Strategies to overcome this pharmacokinetic resistance include co-administering potent ABC transporter inhibitors and developing nanoparticle-based delivery systems designed to bypass efflux pumps (168). Furthermore, second-generation SINE compounds, such as KPT-8602 (Eltanexor), have been developed to address some of these limitations. Eltanexor shows reduced central nervous system penetration and improved tolerability, allowing more frequent dosing schedules that may sustain higher intracellular drug concentrations and reduce the impact of efflux-mediated resistance (169).

Evidence from high-risk multiple myeloma has shown that XPO1 overexpression itself can contribute to resistance (170). Increased target-protein abundance requires higher drug concentrations to fully occupy Cys528 binding sites, allowing residual oncogenic nuclear export activity to persist despite treatment. Moreover, resistance to SINE compounds appears to be a gradual and complex process involving extensive cellular adaptation. Comparative analyses of parental and SINE-resistant cells have identified substantial alterations in signalling pathways, including changes in the expression of genes associated with inflammation, cell adhesion and apoptosis. These findings suggest a broad transcriptional reprogramming response that enables cancer cells to activate compensatory pathways and circumvent the antitumour effects resulting from SINE-induced nuclear retention of tumour suppressor proteins. The persistence of reduced nuclear accumulation of these proteins, together with

sustained alterations in protein expression profiles, further supports adaptive survival mechanisms in resistant cells (171).

Notably, XPO1 overexpression is a common feature of gynaecological malignancies, although XPO1 is also markedly expressed in normal reproductive tissues. A pan-cancer analysis of normal tissues using data from the Genotype-Tissue Expression (GTEx) project demonstrated that elevated XPO1 expression is not restricted to malignant tissues. Expression levels in normal ovarian and uterine tissues were relatively higher than those observed in tissues such as the heart and blood (172). Collectively, these findings indicate that high XPO1 expression is a physiological characteristic of female reproductive organs. However, persistent or further elevated XPO1 expression appears to contribute to tumour progression and chemoresistance in gynaecological malignancies, including ovarian carcinoma.

Pharmacodynamic resistance refers to the ability of tumour cells to tolerate target inhibition by activating compensatory survival mechanisms. Selinexor promotes the nuclear retention of several negative regulators, including Iκα, PTEN and FOXO1/3a, thereby suppressing the NF-κB and PI3K-AKT signalling pathways (173). Nevertheless, SINE-resistant cells have been reported to exhibit markedly elevated basal NF-κB activity. Although Selinexor suppresses NF-κB signalling by retaining Iκα in the nucleus, persistent enhanced basal NF-κB activity suggests adaptive activation of upstream or parallel signalling networks that bypass this XPO1-dependent regulatory checkpoint (174).

In addition, XPO1 inhibition has been shown to induce dose- and time-dependent autophagy in glioblastoma cells. Rather than representing a passive consequence of treatment, this autophagic response functions as a potent cytoprotective mechanism that enables tumour cells to withstand Selinexor-induced stress. Mechanistically, this effect has been linked to nuclear retention of transcription factor EB (TFEB), a recognised XPO1 cargo protein, which activates genes involved in autophagic initiation and maintenance. Notably, both genetic and pharmacological inhibition of autophagy, including chloroquine treatment, markedly enhanced sensitivity to Selinexor, increased apoptosis, and prolonged survival in intracranial mouse models. These findings suggest that targeting treatment-induced autophagy may be a viable strategy to improve the efficacy of SINE compounds (175). This adaptive mechanism may also be relevant to ovarian cancer, in which therapeutic stressors, including cisplatin and SINE treatment, activate ERK signalling and induce autophagy as a survival response (176). However, although TFEB-mediated cytoprotective autophagy has been demonstrated in glioblastoma, its contribution to resistance in gynaecological cancers remains hypothetical and requires further validation.

SINE therapy for overcoming cancer resistance. The tumour microenvironment (TME) contributes to therapeutic resistance by inducing cellular stress responses and promoting immune evasion. In multiple myeloma, the hypoxic bone marrow niche plays a central role in disease progression and resistance to conventional therapies. Notably, Selinexor has demonstrated the ability to overcome this microenvironment-driven resistance. In preclinical models, Selinexor reduced tumour burden and restored sensitivity to bortezomib, with proapoptotic effects being particularly pronounced under hypoxic conditions. These observations indicate that XPO1 inhibition disrupts critical survival pathways supported by the hypoxic TME, supporting the use of Selinexor to restore drug sensitivity in proteasome inhibitor-refractory disease (177).

Beyond its role in adaptation to microenvironmental stress, XPO1 activity has also been implicated in tumour immune evasion. The TME is characterised by the accumulation of regulatory T cells, which suppress effector T-cell function by secreting inhibitory cytokines such as TGF-β and IL-10. At the same time, increased expression of immune checkpoint molecules, particularly PD-L1, promotes T-cell exhaustion and facilitates tumour survival (178). In gynaecological cancer models, XPO1 inhibition has been shown to convert immunosuppressive myeloid-derived suppressor cells into neutrophil-like cells with T-cell-activating properties through nuclear retention of ERK1/2, thereby enhancing antitumour immune responses (179,180).

If elevated XPO1 activity contributes to the establishment of an immune-depleted TME, resistance mechanisms that preserve XPO1 function, including mutation, overexpression or pharmacokinetic drug efflux, may simultaneously maintain an immunosuppressive environment. Consequently, effective strategies to overcome SINE resistance may require integration of nuclear export inhibitors with immunomodulatory therapies, including immune checkpoint blockade, to reverse immune suppression and enhance cytotoxic T-cell activity (181). Supporting this concept, decitabine priming combined with Selinexor significantly reduced tumour burden and ascites formation while enhancing effector T-cell function in ovarian cancer models (182).

High XPO1 expression has also been negatively associated with interferon-γ (IFN-γ) signalling activity (183). IFN-γ exerts complex and context-dependent effects in gynaecological malignancies. In cervical cancer, IFN-γ promotes antitumour immunity by enhancing tumour cell susceptibility to cytotoxic T lymphocyte-mediated killing through upregulation of major histocompatibility complex class I molecules and CD54 expression (184). By contrast, IFN-γ signalling in ovarian cancer may facilitate immune evasion by activating the JAK/STAT1 pathway, increasing expression of PD-L1 and the proto-oncogene BCL3. Furthermore, IFN-γ-induced activation of JAK/STAT1 signalling and proteasomal pathways promotes expression of the non-classical major histocompatibility complex molecule HLA-E, which suppresses natural killer cell-mediated cytotoxicity and is associated with poor clinical outcomes.

XPO1, the principal nuclear export protein, reinforces this resistant phenotype in several malignancies, including ovarian cancer, where its overexpression associates with poor survival and chemoresistance through aberrant nuclear export of tumour suppressor proteins such as p53. Although a direct and universal regulatory relationship between IFN-γ signalling and XPO1 activity has not been established, XPO1 inhibitors such as Selinexor can restore platinum sensitivity in resistant ovarian cancer cells. These findings suggest that IFN-γ-mediated immune escape and XPO1-driven therapeutic resistance represent complementary but mechanistically distinct pathways that collectively enhance ovarian tumour fitness (185).

Selective inhibition of XPO1 using SINE compounds represents an important therapeutic strategy in oncology. However, complex, multifactorial resistance mechanisms constrain the long-term efficacy of this approach. Effectively managing SINE resistance will require a comprehensive strategy that simultaneously addresses genetic, pharmacokinetic, and pharmacodynamic contributors to treatment failure. One promising approach combines SINE compounds with agents that inhibit or counteract compensatory survival pathways activated in response to XPO1 inhibition, restoring therapeutic sensitivity and improving clinical outcomes.

7. Challenges and future perspectives

An imbalance in bidirectional communication between the nucleus and cytoplasm is a common feature of several types of cancer. In gynaecological malignancies, dysregulation of nucleocytoplasmic transport generally results from altered expression of proteins involved in nuclear trafficking. Although these alterations enhance malignant characteristics, including proliferation, invasiveness and therapeutic resistance, they also create novel opportunities for targeted intervention. Despite the identification of numerous natural and synthetic inhibitors of nuclear import and export, only one nuclear export inhibitor, Selinexor, has received FDA approval for treating multiple myeloma and diffuse large B-cell lymphoma. Furthermore, Selinexor has demonstrated encouraging activity in patients with advanced gynaecological cancers, both as monotherapy (135,154) and in combination with paclitaxel and carboplatin (NCT02269293; first registered on ClinicalTrials.gov on 21 October 2014).

Adverse effects associated with Selinexor treatment are generally mild to moderate and can usually be managed with supportive care. Nevertheless, further development of clinically applicable nuclear transport inhibitors may be constrained by limited target specificity. Research has indicated that >1,000 XPO1 cargo proteins have been identified in human cells, including proteins involved in translation, autophagy, signal transduction, kinase regulation and phosphatase activity (186). Consequently, XPO1 functions as a central regulator of multiple cellular processes that govern both survival and cell death. For regulatory proteins, inhibition of nucleocytoplasmic transport may be rapidly bypassed through activation of compensatory signalling networks. Given the extensive number of XPO1 cargoes affected, it remains difficult to identify the principal determinants of cell survival or to define the precise mechanisms underlying the antitumour activity of XPO1 inhibitors.

Additional complexity arises from increased drug efflux and TME-mediated interactions, both of which contribute to therapeutic resistance. Notably, XPO1 inhibition has been reported to increase tumour heterogeneity under certain conditions, potentially creating further challenges for durable treatment responses (187). Another important limitation relates to the chemical properties of current nuclear transport inhibitors. Most known nuclear export inhibitors are covalent compounds, making them susceptible to off-target interactions through non-specific bond formation (102). Therefore, future research should prioritise developing non-covalent SINE compounds, which may offer improved specificity while overcoming mutation-driven resistance associated with alterations in XPO1 (188).

Combining SINE compounds with other anticancer agents may be an effective strategy to overcome treatment resistance. The PI3K signalling pathway is frequently mutated and hyperactivated in gynaecological cancers, and several PI3K inhibitors have been clinically evaluated, with some demonstrating promising therapeutic activity (189,190). Notably, SINE compounds may counteract PI3K-mediated resistance mechanisms. Inhibition of nucleocytoplasmic transport promotes nuclear retention of tumour suppressor proteins such as FOXO. Nuclear localisation restores FOXO transcriptional activity and stimulates PTEN expression, a negative regulator of the PI3K/AKT pathway. Through this mechanism, SINE compounds may function as potent modulators of therapeutic resistance and serve as valuable components of combination treatment strategies (119).

XPO1 inhibition has already been shown to enhance the efficacy of standard first-line chemotherapeutic agents, including cisplatin and paclitaxel, in gynaecological cancers. With regard to targeted therapies, PARP inhibitor treatment, which is widely used in ovarian cancer, may also benefit from concurrent XPO1 inhibition; however, direct validation of this strategy in ovarian cancer remains limited (161). Notably, beyond its direct cytotoxic activity, Selinexor has also been reported to exert anti-inflammatory effects. These properties may offer additional therapeutic opportunities and support the investigation of combination regimens that incorporate both XPO1 inhibitors and anti-inflammatory agents as part of future anticancer strategies (191).

Although cargo-specific nuclear import inhibitors are likely to cause fewer side effects than importin inhibitors, the complexity of nuclear import machinery still limits their clinical development. Most cargoes lack druggable binding sites because NLSs are short, flexible peptide motifs. There are no flat surfaces or protein 'pockets' for an inhibitor to bind, and there is no specificity, as NLSs of different cargoes share sequence similarity. Additionally, cargo can utilize several NLSs or import to the nucleus can be NLS-independent. A classic example is tumour suppressor p53, which has several NLS sequences. The main NLS used to enter the nucleus is homologous to NLSs on other nuclear proteins; however, NLS-deprived wild-type p53 can also be imported into the nucleus in a complex with SV40 (192). Occasionally, NLS cannot be readily targeted by small-molecule compounds because an inhibitor protein masks the NLS, which is exposed only after protein activation; this is the case of NF-κB, which was discussed earlier. Finally, blocking the import of an individual protein may be less appealing from a commercial perspective, as the therapeutic benefit is likely to be confined to cancers that specifically depend on that protein rather than a variety of tumours. On the other hand, blocking XPO1 stops the nuclear export of several suppressors; thus, it can be applied to treat different types of cancer.

To overcome these obstacles, the development of nuclear import inhibitors should expand beyond conventional approaches. Stapled peptides that could easily bind flat protein surfaces (193), single-domain antibodies that bind cargo with high specificity and mask its NLS sequence (194) or molecular glues that prevent cargo import by stabilizing

its cytosolic conformation and NLS exposure (195) are all alternative therapeutic modalities that could be exploited for nuclear import inhibition. Clinical development of cargo-specific nuclear import inhibitors would benefit from studies evaluating cargo expression levels in gynaecological tumours, as well as identifying gynaecological cancer subtypes that are particularly dependent on the nuclear localization of individual cargos.

Transportins showing markedly elevated expression in gynaecological cancers have been recognized as potential tumour markers (Table I). Notably, researchers have detected increased protein or circular RNA concentrations not only in tumour tissue but also in patient blood samples, creating opportunities for minimally invasive diagnostics (70,76,81). Thus, targeting nuclear transport has potential not only for developing new transformative anticancer therapies but also for improving gynaecological cancer screening.

Additionally, clinical practice would benefit from reliable biomarkers that would help predict patient sensitivity to nucleocytoplasmic inhibitors. Several candidates for Selinexor sensitivity have been identified in multiple myeloma, including transporter ABCC4 (196) and a three-gene signature *WNT10A-DUSP1-ETV7* involved in interferon-mediated apoptosis (197); however, data on gynaecological tumours remain limited. In addition, some studies promote repurposing of ivermectin for the treatment of gynaecological cancer, mostly in combination with other first-line anticancer drugs (139,198). This should be carefully considered, as these findings are based on *in vitro* models and lack clinical validation (199).

Current evidence suggests that circulating nuclear transport proteins, including KPNB1, XPO1 and IPO7, are promising candidate biomarkers for gynaecological cancers because they are associated with tumour progression and can be detected through minimally invasive procedures. However, available evidence remains largely limited to discovery and early validation, highlighting the need for larger clinical studies to establish their diagnostic and prognostic utility. Although XPO1 currently has the strongest clinical relevance, because selective inhibitors such as selinexor have entered clinical trials (119), several challenges currently limit their translation into routine clinical screening. Most studies in gynaecological cancers have been conducted in relatively small cohorts and lack independent validation in larger populations. In addition, because these proteins participate in essential nucleocytoplasmic transport pathways and are dysregulated across multiple malignancies and non-malignant biological processes, their cancer specificity remains a major challenge for clinical translation. Furthermore, it remains unclear whether circulating levels of proteins originate directly from tumour cells or other physiological sources (20).

To establish their clinical utility, further validation is required through large, multicentre studies with external validation cohorts. Future work should include analyses to determine whether circulating nuclear transport proteins can detect early-stage disease or predict recurrence. Analytical validation is also essential to demonstrate assay accuracy, reproducibility, and standardized clinical thresholds. Finally, since single biomarkers rarely achieve sufficient diagnostic accuracy, comparative studies should evaluate whether combining KPNB1, XPO1, IPO7, and related proteins with existing biomarkers improves diagnostic sensitivity and specificity sufficiently for clinical implementation. Given the complexity and heterogeneity of gynaecological cancers, these proteins are more likely to achieve clinical utility as components of biomarker panels rather than standalone screening markers (119). In summary, the most notable evidence gap is the lack of large-scale prospective serum validation studies demonstrating the diagnostic performance of nuclear transport proteins for screening and early detection of gynaecological cancers.

8. Conclusions

In conclusion, dysregulated expression of nuclear transport proteins contributes to aberrant nucleocytoplasmic trafficking in endometrial, cervical and ovarian cancers. This leads to the development of malignant cell phenotypes, including enhanced cell proliferation, migration, and resistance to therapy. In this context, SINEs have emerged as a promising class of targeted therapeutic agents, with growing evidence supporting their clinical utility.

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Competing interests

The authors declare that they have no competing interests.

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