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Exportin 1 inhibition as antiviral therapy

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Coronavirus 2019 (COVID-19; caused by Severe Acute Respiratory Syndrome Coronavirus 2; SARS-CoV-2) is a currently global health problem. Previous studies showed that blocking nucleocytoplasmic transport with exportin 1 (XPO1) inhibitors originally developed as anticancer drugs can quarantine key viral accessory proteins and genomic materials in the nucleus of host cell and reduce virus replication and immunopathogenicity. These observations support the concept of the inhibition of nuclear export as an effective strategy against an array of viruses, including influenza A, B, and SARS-CoV. Clinical studies using the XPO1 inhibitor selinexor as a therapy for COVID-19 infection are in progress.

Introduction

The COVID-19 pandemic has led to most of the world's human population being placed in quarantine. COVID-19 is caused by SARS-CoV-2, which is a positive-sense single-stranded RNA virus. The infection is often complicated by a marked inflammatory response, which, in turn, can lead to multiorgan dysfunction, respiratory failure, and death [1]. There is no established effective therapy for SARS-CoV-2 infection, indicating an acute and urgent need for new drugs or vaccines [2]. Influenza A and B viruses, as well as the other coronavirus species that cause SARS and Middle-East Respiratory Syndrome (MERS), require several accessory proteins to guide replication and mediate pathogenicity. Examples of these proteins include influenza A virus nucleoprotein, SARS-CoV ORF1a/b, SARS-CoV ORF3a/b, and MERS-CoV ORF4a [3–7]. Some of these viral proteins shuttle between the host cell nucleus and cytoplasm aided by specialized transporters belonging to the karyopherin family [8,9]. Earlier studies showed that nuclear export inhibitors (originally developed as anticancer agents) could retain SARS-CoV and MERS-CoV accessory proteins in the nucleus of host cells, thereby suppressing their virulence and pathogenicity [10]. The genome of SARS-CoV-2 is 80% identical to that of SARS-CoV [11] and large-scale trials with nuclear export inhibitor are ongoing for the treatment of patients with COVID-19. If this approach is shown to be effective against SARS-CoV-2, then future work could focus on other viral infections, including influenza A and B.

Nucleocytoplasmic transport is important for the proper functioning of cells

Organized trafficking of key proteins, such as p53, Forkhead box O (FoxO), IκB, and RNAs (e.g., a subset of messenger, micro, and transfer RNA) between the nucleus and cytoplasm is an essential cellular process. Spatial distribution is mediated, in part, by nucleocytoplasmic transport and is essential for proper protein function [12]. Any entity >40 kDa moves between the nucleus and cytoplasm with the help of specialized transporters [13]. The import of proteins from the cytoplasm to the nucleus is governed by importins that recognize the nuclear localization signal (NLS) in the cargo. By contrast, the export of proteins from the nucleus is mostly regulated by XPO1, also known as chromosome region maintenance 1 (CRM1). With the help of Ran-GTP, XPO1 binds to the cargo protein through the recognition of a nuclear export signal (NES). The conversion of Ran-GTP from Ran-GDP occurs in the nucleus facilitated by Ran-guanine nucleotide exchange factor (Ran-GEF) [14]. Hundreds of cellular proteins and many viral accessory proteins carry XPO1-recognizable NES (Fig. 1) [10]. Studies have shown that, in cancer, XPO1 is universally hyperactive, causing the unusual export of important tumor suppressors to the cytoplasm, leading to their functional inactivation. Drugs in the Selective Inhibitors of Nuclear Export (SINE)

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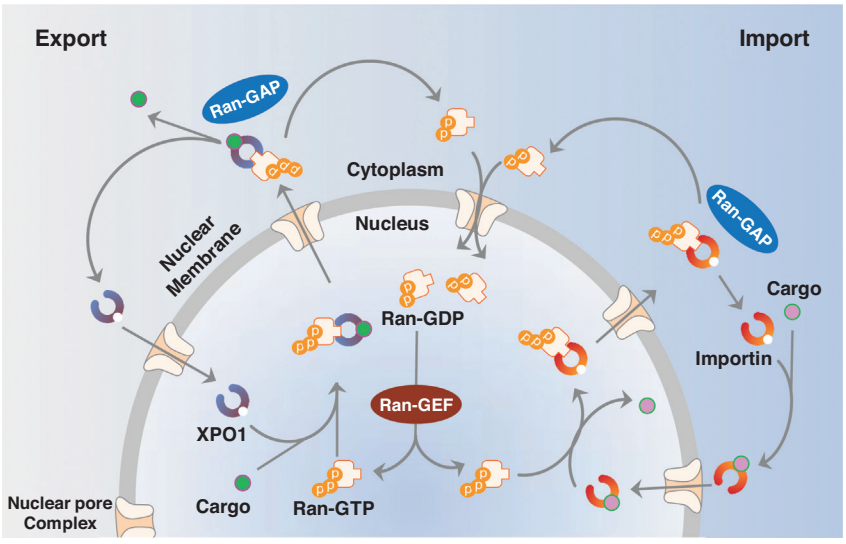

FIGURE 1

Schematic representation of nuclear export and import mechanism. During the export process, the nuclear Ran guanine exchange factor (Ran-GEF) phosphorylates Ran-GDP to form Ran-GTP. Upon activation, Ran-GTP binds to exportin-1 (XPO1), which enables the binding of nuclear export signal (NES) containing cargo protein with XPO1, forming the Ran-GTP-XPO1-Cargo complex. The export complex is shuttled to the cytoplasm through the nuclear pore complex (NPC). In the cytoplasm, the complex dissociates by the hydrolytic action of Ran GTPase-activating protein (Ran-GAP) and XPO1 and Ran-GDP return to the nucleus. During the import process, the importin binds to cargo proteins containing the nuclear localization signals (NLS). The importing cargo complex then directly shuttles to the nucleus through NPC. In the nucleus, Ran-GTP interacts with cargo-bound importin and facilitates the release of cargo protein. Ran-GTP bound protein importin exits the nucleus and dephosphorylated by the action of Ran-GAP.

family, including selinexor (KPT-330 or XPOVIO^{R}) and related agents verdinexor (KPT-335) or KPT-350, can efficiently block XPO1-mediated nuclear export, thereby preserving the nuclear localization (and resultant functionality) of tumor suppressors [15]. These SINE compounds have a similar structure (Fig. S1 in the supplemental information online) and interact with the Cys528 residue of XPO1 at the NES-binding pocket. The absence of long hydrolyzable side chain enables the gradual reversibility of inhibition, which confers reduced toxicity [16]. Among SINEs, selinexor has been evaluated in several Phase I, II, and III studies and received US Food and Drug Administration (FDA) approval for penta-refractory multiple myeloma [17]. Beyond its role in normal cellular homeostasis and cancer cell survival, XPO1 is relevant in other disease states, including viral infections [10]. Therefore, it is conceivable that XPO1 inhibitors developed as anticancer agents could have other applications. Here, we focus on previous work and ongoing trials evaluating the potential antiviral activity of XPO1 inhibitors.

NLS/NES determine the subcellular distribution of viral proteins

Viral proteins can localize in the cytoplasm, nucleus, and/or nucleolus depending on multiple signal sequences [18] and cell cycle phases [19]. Specific viral proteins, such as CoV spike (S), matrix/membrane (M), and envelop (E) proteins, are localized in the endoplasmic reticulum–Golgi intermediate compartment (ERGIC) because of the presence of Golgi or ER-retrieval signals [20,21]. Regulated localization of viral proteins is essential for efficient replication of virus particle and virion assembly [22]. In infectious bronchitis virus (IBV, an avian coronavirus) infection, the viral nucleocapsid (N) protein is localized both in the cytoplasm and nucleolus of the infected cells [18,23]. The IBV N protein contains an eight amino acid-long nucleolar localization/retention signal (NoRS) motif at its N-terminal domain, the functionality of which appears to be dependent on the presence or absence of other viral proteins in the cytoplasm [18]. It has been speculated that such nucleolar localization is a viral strategy to control single guide (sg)RNA synthesis [24]. Research has demonstrated that CoV N proteins contain NLS and can be localized in the cytoplasm and/or nucleolus [19]. Subcellular localizations can be modulated by other molecular events. For example, SARS-CoV N protein is mostly distributed to the cytoplasm, although it has eight NLS and at least one NoRS. Despite these signal sequences, accessibility to nuclear import machinery might be limited because of phosphorylation or conformational restraints [23].

The proteins and mechanisms determining the localization of viral proteins to the cytoplasm, nucleus, or nucleolus are not conserved among virus families [25]. Proteins lacking NES can bind to an adaptor protein, which in turn can facilitate nuclear export. For example, nuclear export of SARS-CoV N protein occurs through phosphorylation-dependent binding to regulatory protein 14-3-3. Inhibition of 14-3-3 protein increased the nuclear accumulation of SARS-CoV N protein [26]. In other instances, the presence of a NES sequence in some viral proteins leads to export to the cytoplasm. Sequence analysis confirmed the presence of NES in SARS-CoV 9b protein at amino acid positions 46–54 (^{46}LRLGSQLSL^{54}) [27]. Analysis of SARS-CoV-2 proteins revealed that several proteins, including the nucleocapsid phosphoprotein (NP), nonstructural protein-9 (NSP9), fundamental component of replication, the NSP12 (RNA-dependent RNA polymerase, RdRp) [28], spike glycoprotein (SG), membrane glycoprotein (MG), envelope protein (EP), and open reading frame 3a (ORF3a), have sequences predicted to function as NESs (Table 1) (NetNES 1.1 server; www.cbs.dtu.dk/services/NetNES/). Furthermore, angiotensin-converting enzyme 2 (ACE2) protein, the functional receptor for SARS-CoV-2 entry into human cells, contains a predicted NES sequence. These observations hold significance

TABLE 1

NES consensus sequences in viral and human proteins

Virus	Protein	Sequence[a]	Refs
Consensus		Φ1 X2–3 Φ2 X2–3 Φ3 X Φ4	
SARS-CoV-2	NSP9	^{46}LALLSDLQDL^{55}[b]	www.cbs.dtu.dk/services/NetNES/
	NPP	^{223}LLDRLNQL^{230}[b]	www.cbs.dtu.dk/services/NetNES/
	SG	^{242}LEPLVDLPI^{250}[b]	www.cbs.dtu.dk/services/NetNES/
	MG	^{134}LESELVIGAVIL^{145}[b]	www.cbs.dtu.dk/services/NetNES/
	EP	^{31}LAILTALRL^{39}[b]	www.cbs.dtu.dk/services/NetNES/
	ORF3a	^{77}VHFVCNLLL^{85}[b]	www.cbs.dtu.dk/services/NetNES/
	NSP12 (RdRp)	^{853}LMIERFVSLAI^{864}[b]	www.cbs.dtu.dk/services/NetNES/; http://prodata.swmed.edu/LocNES/LocNES.php
SARS-CoV	ORF3b	^{76}LHKLLQTLVF^{86}	[5] www.cbs.dtu.dk/services/NetNES/
	ORF9b	^{46}LRLGSQLSL^{54}	[27]
IAV	NSP1	^{138}FDRLETLIL^{146}	[55]
	NSP2	^{12}ILMRMSKMQL^{21}	[55]
	NSP2	^{31}MITQFESLKL^{40}	[55]
	NP	^{32}MIDGIGRFYI^{41}	[55]
	NP	^{183}VKGVGTMVM^{191}	[55]
	NP	^{256}LIFLARSALIL^{266}	[6,55]
	M1	^{59}ILGFVFTLTV^{68}	[55]
HIV-1	PKI	^{35}LNELALKLAGLDI^{47}	[56]
	Rev	^{73}LQ LPPLERLTL^{83}	[56]
BIV	Rev	^{112}LKDLVRHMSL^{121}	[57]; www.cbs.dtu.dk/services/NetNES/
HTLV	Rex	^{80}MDALSAQLYSSLSL^{93}	[57]
FIV	Rev	^{101}MTDLEDRFRKLFGS^{114}	[57]
Human protein	ACE2	^{753}IVVGIVILIFTGI^{765}[b]	www.cbs.dtu.dk/services/NetNES/; http://prodata.swmed.edu/LocNES/LocNES.php

Abbreviations: BIV, bovine immunodeficiency virus; FIV, feline immunodeficiency virus; HTLV, human T-cell leukemia-lymphoma virus; IAV, Influenza A virus; M1, matrix protein 1; NPP, nucleocapsid phosphoprotein; NS, non-structural protein; PKI, protein kinase A inhibitor; REV, HIV-1 regulatory protein; REX, HTLV RNA binding protein.

[a] NES consensus sequence, Φ1-(x)2–3-Φ2-(x)2–3-Φ3-x, where X is an amino acid that is preferentially charged, polar, or small. Hydrophobic (Φ) residues [e.g., leucine (L), isoleucine (I), valine (V), phenylalanine (F) and methionine (M)] in the NES consensus sequence are underlined.

[b] Predicted NES sequences from NetNES 1.1 or LocNES server developed by the bioinformatic unit at Technical University of Denmark and UT Southwestern Medical Center respectively.

and also indicate that the spatial distribution of these virus-associated proteins could be influenced through XPO1 inhibition.

XPO1-mediated protein or RNA export is necessary for viral replication

XPO1 is utilized by a diverse array of viruses at different steps of their lifecycle (Fig. 2) [29]. Viruses have been shown to hijack the nuclear transport machinery to mislocalize host cell proteins along with the proper localization of its own proteins [30]. Thus, specific inhibition of XPO1 might impair the ability of the virus to replicate and, in principle, could represent a broadly effective therapy against viral infections. XPO1 inhibition affects the expression of virion protein, imperfect assembly, overall multiplication rate, and a reduction in infectiousness, as well as modulating the host immune responses against the virus [10]. Recently, XPO1 was recognized as a 'hub' host protein for SARS-CoV multiplication [31]. Similarly, SARS-CoV-2-human protein interactome analysis showed that inhibition of XPO1 was able to disrupt the interaction of SARS-CoV-2 ORF6 protein with human protein ribonucleic acid export 1 (RAE1) [2]. Along the same lines, previous research demonstrated that XPO1 inhibition reduces replication of other viruses, including influenza A and B viruses and respiratory syncytial virus (RSV), by affecting the nuclear export of proteins essential for the viral lifecycle [32]. Inhibition of XPO1 was also shown to be efficacious against pandemic H1N1 (A/California/04/09), the highly pathogenic H5N1 avian influenza strain, and previously emerged H7N9 *in vitro* [32,33]. Additionally, *in vitro* and *in vivo* experiments showed that the XPO1 inhibitor verdinexor reduced viral titer, induced accumulation of viral ribonucleoprotein (vRNP) in the nucleus, and altered cytokine expression with resultant improvement in lung pathology and fewer animal deaths because of infection with influenza viruses, including pandemic H1N1 and H3N2 (A/Philippines/2/82) [32,34].

The effects of XPO1 inhibition in RSV infection are of particular interest. Unlike influenza viruses, RSV causes severe lower respiratory tract infections affecting younger or older adults, especially those who are immunocompromised. It has been shown that matrix protein of RSV contains NES and remains inside the nucleus at an early stage of replication. During the later stage of infection, M protein is exported to the cytoplasm for the virus assembly. Experimentally induced retention of viral M protein in the nucleus by leptomycin B (LMB, an irreversible inhibitor of XPO1; Fig. S1 in the supplemental information online) or by verdinexor resulted in a significant reduction in RSV titers *in vitro* [35,36]. Inhibition of XPO1 using LMB also resulted in nuclear accumulation of SARS-CoV 9b protein, which activates caspase 3-induced apoptotic cell death in mammalian cells after transient transfection. The finding was confirmed using both general caspase inhibitor (Z-VAD-FMK) and a specific caspase 3 inhibitor (Z-DEVD-FMK). Furthermore, XPO1 inhibition was able to initiate cytoplasmic degradation of the SARS-CoV 9b protein, which is essential for the viral lifecycle [8]. As another example, the NES-containing HIV-1-encoded Rev protein controls unspliced or partially spliced mRNA export. XPO1 inhibition with synthetic inhibitors (PKF050-638 and *N*-azolylacrylates) blocked Rev protein nuclear export and reduced HIV-1 production in latently infected cells [37,38]. In the same way, forced nuclear retention of non-structural protein 5 (NS5) of dengue virus, hUL47 tegument protein of herpes simplex virus 1 (HSV-1), phosphoprotein 65 (pp65) of human cytomegalovirus (HCMV), and ORF3b protein of SARS-CoV altered the kinetics of virus production across each of these viral types [34].

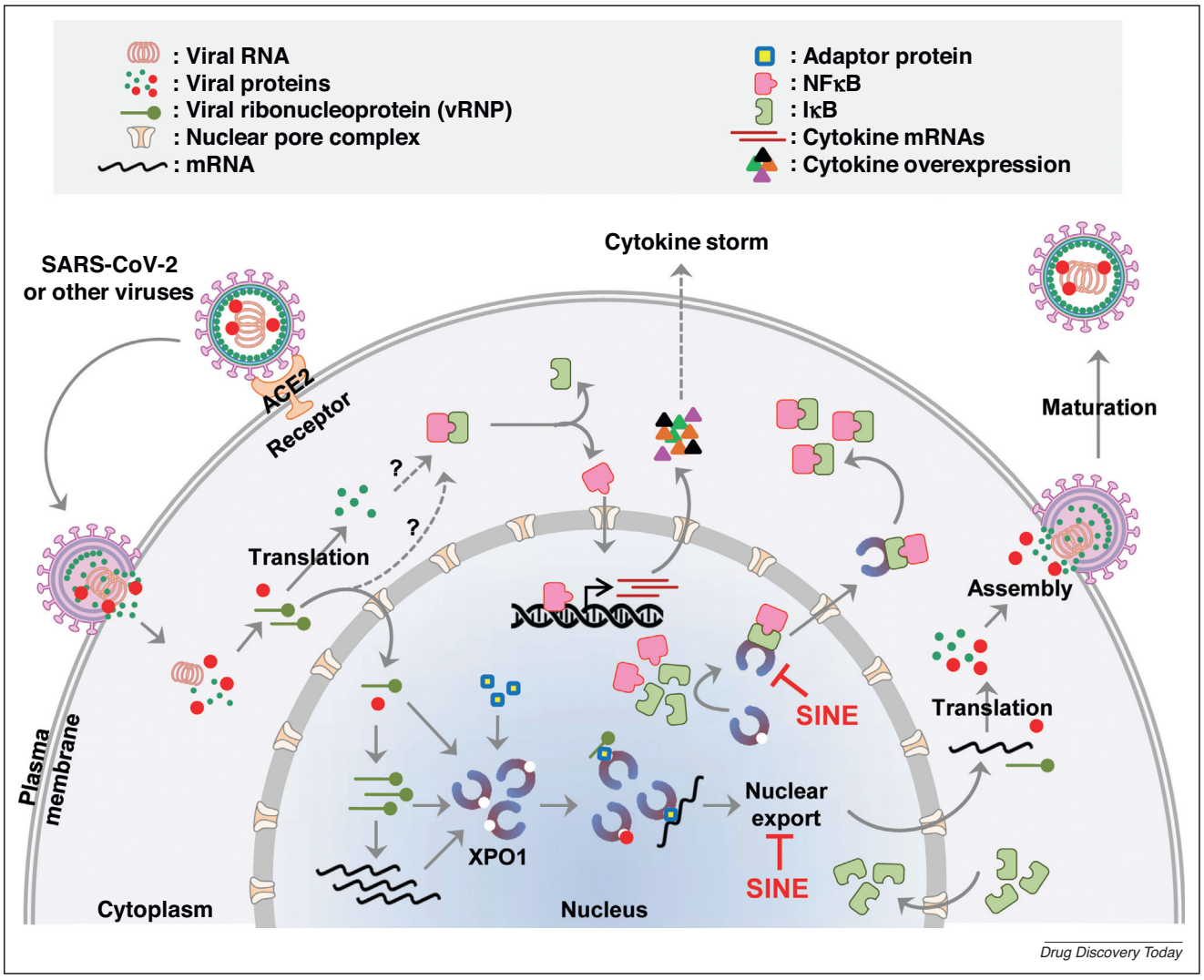

FIGURE 2

Proposed role of exportin-1 (XPO1) in the transport of genetic material and proteins of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or other viruses and in the regulation of immune response. Upon attachment to angiotensin-converting enzyme 2 (ACE2) receptors, expressed on the surface of the plasma membrane, the virus releases its genetic materials and proteins into the cytoplasm. The viral ribonucleoproteins (vRNP) and other associated proteins can be imported into the nucleus for multiplication and synthesis of mRNA. Several viral proteins might also enter into the nucleus for genomic regulation. Viral genetic materials and proteins require XPO1-mediated nuclear export for proper replication. In cytoplasm, viral genetic materials or proteins can activate proinflammatory molecules, such as nuclear factor kappa B (NF-κB) [52–54]. Activated NF-κB enters the nucleus and induces the expression of several proinflammatory cytokines. The overexpressed cytokines can contribute to a cytokine storm. Selective inhibitors of nuclear export (SINE) compounds, such as selinexor or verdinexor, can block the XPO1-mediated nuclear export of vRNPs, viral mRNAs, thereby inhibiting late-stage assembly processes. Moreover, SINE compounds can block the nuclear export of IκB, which results in accumulation in the nucleus. The higher level of IκB allows inhibition of NF-κB and a subsequent reduction in proinflammatory signaling. Dotted arrow indicates unknown mechanism.

XPO1 is also involved in the export of different RNAs, and this might also have relevance for the treatment of viral infections. Inhibition of XPO1 halts the transcription of HIV-1 by blocking viral RNA transport, preventing the production of new HIV-1 virions [34]. This was validated in HIV/AIDS-related lymphoma models, where selective inhibitor of nuclear export (SINE)-mediated nuclear export inhibition was shown to prevent transport of late intron-containing HIV RNA species to the cytoplasm, resulting in a reduction in viral replication [39]. The role of XPO1 was confirmed by CRISPR/Cas9 genome editing, where introduction of a SINE-resistant XPO1 mutation (C528S) abrogated the effects of SINEs on viral replication [39]. As another example, SINE triggered the retention of tumor suppressor protein p53 in the nucleus as well as the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) activity via IκB in primary effusion lymphoma (PEL) cells, causing arrest of the cell cycle and enhanced apoptotic cell death. These results suggest targeting of XPO1 as an innovative and broad-range effective therapy against a diverse family of viruses that utilize XPO1 pathway for their multiplication.

XPO1 contributes to host immunopathology during viral infection

Virus-associated immunopathology, as observed in influenza virus, MERS-CoV, and so on, involves the release of proinflammatory cytokines through the activation of NF-κB (IκB) signaling [7,35,40]. Excessive activation of NF-κB signaling correlates with the development of

acute respiratory distress syndrome (ARDS). The ORF4a and ORF4b proteins of MERS-CoV are localized mostly in the nucleus and activate NF-κB signaling and the interferon type I (IFN-1) promoter [40,41]. Importantly, recent genomic and molecular analyses showed that SARS-CoV-2 ORF9c protein interacts with various proteins that regulate IκB kinase and NF-κB signaling, including NLR Family Member X1 (NLRX1), coagulation factor II (thrombin) receptor-like 1 (F2RL1), and NEDD4 family-interacting protein 2 (NDFIP2) [2]. For sustained activation of NF-κB, efficient nuclear export of its regulator IκB is necessary. The XPO1 inhibitor KPT-350 (another SINE compound) was demonstrated to prevent IκB nuclear export (Fig. 2) and is now in preclinical evaluation of its anti-inflammatory properties [35]. Mechanistically, SINE compounds block the phosphorylation of IκB-α and the NF-κB p65 subunit [42] and inhibit copper metabolism domain-containing 1 (COMMD1) and FoxO exports [43] to suppress NF-κB activity. Suppression of the NF-κB pathway leads to a reduction in cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNFα) [44]. Indeed, KPT-350 has been shown to upregulate anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13, and to downregulate proinflammatory cytokines, including IL-1A/B, IL-6, and IL-18, in a rat traumatic brain injury model [45]. Based on this evidence, it can be reasonably postulated that blocking XPO1-dependent cytokine production would reduce virus-associated immunopathology.

Huang *et al.* observed a correlation between SARS-CoV-2 disease severity and the level of cytokines or other factors, such as, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon-γ (IFNγ) inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1α (MIF-1α), and TNFα [46]. Analysis of 150 SARS-CoV-2 cases in Wuhan, China, demonstrated elevated IL-6 levels as an independent predictor of mortality ($P < 0.0001$) [47]. This 'cytokine storm' was postulated to provoke ARDS, single or multiple organ failure, and eventually death. In an endotoxin-induced sepsis mouse model in which animals experienced respiratory insufficiency (ARDS) similar to that seen in SARS-CoV-2, selinexor was shown to increase the survival at doses $\geq$15 mg/m^2 [44]. Perwitasari *et al.* demonstrated that verdinexor reduced the expression of inflammatory cytokines, inflammation, and viral pathology in influenza virus-infected mice [32]. Verdinexor not only limited viral shedding, but also reduced proinflammatory cytokine expression and leukocyte infiltration into the bronchoalveolar space in this model and also in another animal model (ferrets) [32]. Collectively, there are multiple lines of evidence supporting the utility of SINE compounds as antiviral agents. Considering the similarities in the inflammatory processes associated with SARS-CoV, influenza viruses, and SARS-CoV-2, SINE compounds could be an effective strategy to mitigate cytokine dysregulation in patients with COVID-19 (Fig. 2). Thus, as clinical testing of SINEs as potential antiviral agents proceeds, it will be important to study the effects on both viral replication and production of inflammatory cytokines.

XPO1 facilitates the function of viral antagonistic proteins

Viral pathogenesis and virulence are regulated by several antagonistic proteins encoded by the virus itself, typically interfering with host IFN signaling. This can delay infection recognition by host cells, innate immune sensing, and the activity of many signaling pathways. Among the extremely pathogenic RNA viruses, SARS-CoV ORF6 protein was shown to block nuclear import by inhibiting karyopherin-α2 in the cytoplasm. Studies of infected primary cultures of human respiratory tract epithelial cells demonstrated that ORF6 protein expression attenuates the functions of transcription factors, including cAMP-responsive element-binding protein 1 (CREB1), vitamin D receptor (VDR), signal transducer and activator of transcription 1 (STAT1), mothers against decapentaplegic homolog 4 (SMAD4), p53, endothelial PAS domain-containing protein 1 (EpasI), and octamer-binding transcription factor 3/4 (Oct3/4), which are crucial for the establishment of antiviral responses [48,49]. Similarly, Ebola virus secondary matrix viral protein-24 (VP24) binds to karyopherin-α1 in cytoplasm and blocks STAT1 nuclear import [49,50], indicating a way to achieve IFN antagonism. Importantly, many of these targets, such as STAT1 and SMAD4, are recognized NES-containing cargoes of XPO1 [51]. Recent findings identified interactions between SARS-CoV-2 ORF6 and an IFN-inducible mRNA nuclear export complex, NUP98-RAE1, with high statistical confidence. Interestingly, this study showed inhibition of this interaction by a XPO1 inhibitor [2].

Application of XPO1 inhibitor in the clinic for patients with COVID-19

In view of these observations, two Phase II randomized studies have been initiated to evaluate the activity and safety of low-dose oral selinexor in patients with COVID-19. One is a single-blind placebo-controlled study (ClinicalTrials.gov NCT04349098) in which patients with severe SARS-CoV-2 infection receive either placebo or selinexor at 20 mg on days 1, 3, and 5 each week for 2–4 weeks. The other trial is an open-label study (NCT04355676) in which patients with moderate to severe SARS-CoV-2 infection receive selinexor either 20 mg on days 1, 3, and 5 or 40 mg on days 1 and 3 only. Both the studies are expected to complete enrollment by the end of August 2020. These clinical studies would be the first to evaluate an XPO1 inhibitor as treatment for patients with severe viral infections. The doses of selinexor are significantly lower than the currently approved dose in patients with relapsed multiple myeloma. On a cautionary note, approximately half of the patients receiving selinexor as cancer therapy in clinical trials experienced an infection during the course of therapy, including some with respiratory complications. Specifically, upper respiratory tract infection, pneumonia, and sepsis of any grade occurred in 21%, 13%, and 6% of the patients respectively. The most frequently stated Grade 3+ infections were pneumonia (in 9% of patients) and sepsis (in 6% of patients). On average, these infections occurred after 2–3 months of therapy, which is longer than the duration of SINE exposure on either of the SARS-CoV-2 trials. Furthermore, it is important to take into consideration that patients with relapsed myeloma are typically immunosuppressed. For all of these reasons (dose, duration of therapy, and comorbidity), it is reasonable to hope that patients with COVID-19 might not experience the same frequency or severity of toxicities seen in trials involving patients with cancer. Verdinexor has been tested in a Phase I clinical trial in healthy volunteers and was found to have an improved adverse effect profile (NCT02431364); thus, it might represent an alternative to selinexor if toxicity turns out to be an issue in patients with COVID-19.

Concluding remarks

Treatment of viral infections, similar cancer, requires a nuanced understanding of cell biology and host response. The SINE compound selinexor has received FDA approval as therapy for refractory multiple myeloma, and is being studied in other hematological malignancies and solid tumors. As summarized earlier, there is ample evidence of the role of nuclear transport in viral pathology. Thus, targeted nuclear export inhibition could hold promise as antiviral therapy. Targeting the XPO1 of the host cell with a SINE compound has been shown to attenuate viral replication by blocking the nuclear export

of key viral proteins for different viruses. Additionally, the effects of these compounds on elaboration of proinflammatory cytokines in response to viral infection could mitigate many of the symptoms of severe viral infection. However, whether this will translate into an effective means to treat COVID-19 remains to be seen. Two clinical studies involving low-dose selinexor administration in patients hospitalized with COVID-19 are ongoing and are anticipated to be completed soon. These trials, if positive, could establish a new paradigm for treating viral infections, although this would need to be explored further against other viruses in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.drudis.2020.06.014.

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