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Manipulation of Host Nuclear Transport Pathways in Fungal Infections: Current Evidence and Future Directions

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ABSTRACT

The nuclear pore complex, a large multiprotein structure embedded in the nuclear envelope of eukaryotic cells, serves as the only communication channel between the cytoplasm and the nucleus. Defects in proper nucleocytoplasmic transport are associated with cancers and neurodegenerative disorders. Proper nucleocytoplasmic transport also plays a key role in regulating host immune responses. Viral and bacterial pathogens are known to evade the host immunity by altering the crucial exchange of molecules across the nuclear pore complex. However, whether the mammalian fungal pathogens alter the host nuclear transport machinery to establish infection remains largely unknown. In this review, we present an overview of how mammalian viral and bacterial pathogens manipulate nuclear transport to evade host immunity using a few well-studied examples. We then discuss plant fungal pathogens that are known to manipulate the flow of immunity-related molecules across the nuclear pore complex. Finally, we discuss the mammalian fungal pathogens, in which host nucleocytoplasmic transport plays a key role in host immunity. The fungal manipulation of host nuclear transport remains largely unexplored. However, we argue that this lack of evidence should be treated as a substantial knowledge gap and that these mechanisms should be explored in depth in the future to develop new antifungal strategies.

Keywords: Nuclear transport, nuclear pore complex, Fungal infection, viral infection, bacterial infection

Introduction

The nuclear envelope is a characteristic feature of eukaryotic cells and serves as both a physical barrier and a regulatory interface between the nucleus and cytoplasm. It is composed of two concentric lipid bilayers, namely, the outer nuclear membrane, which is continuous with the endoplasmic reticulum, and the inner nuclear membrane, which is lined by the nuclear lamina. The nuclear lamina, formed primarily by A- and B-type lamins and associated proteins, provides structural support to the nucleus, maintains nuclear shape, and contributes to chromatin organization and gene regulation [1]. Embedded within the nuclear envelope are nuclear pore complexes (NPCs), which perforate the double membrane and provide the sole gateways for macromolecular exchange between the nucleus and cytoplasm. In addition to protecting the genome, the nuclear envelope actively participates in cellular signalling, genome stability, and transcriptional regulation, positioning it as a dynamic regulatory structure rather than a static boundary [2].

Nucleocytoplasmic transport is mediated by NPCs, which are large multiprotein assemblies composed of multiple copies of approximately thirty different nucleoporins arranged in an eightfold-symmetric architecture. A subset of nucleoporins contains phenylalanine–glycine(FG) repeat domains, which form a selective permeability barrier within the central channel of the pore [3]. Small molecules can diffuse freely through this barrier, whereas larger proteins and ribonucleoprotein complexes require active transport mediated by nuclear transport receptors. These receptors, primarily involving importins and exportins, recognize cargos bearing nuclear import or export signals and transport them through the NPC. Directionality of transport is governed by the Ran GTPase cycle, which establishes a gradient of RanGTP and RanGDP in the nucleus and cytoplasm, respectively. This gradient ensures that cargo is properly released and that transport receptors are recycled, allowing nuclear transport to function as a highly regulated, energy-dependent process that controls access to the genome and coordinates cellular responses [4].

Defects in the nuclear transport processes are linked to many diseases, highlighting their essential role in maintaining cellular homeostasis. In some cancers, altered expression or activity of nuclear export receptors, such as exportin-1, leads to cytoplasmic mislocalization of tumour suppressors and transcriptional regulators, promoting oncogenic signalling and disease progression. Importantly, drugs that inhibit exportin-1 have shown clinical benefits in haematological malignancies, underlining the therapeutic potential of targeting the nuclear transport. Abnormal nucleocytoplasmic trafficking is also increasingly associated with neurodegenerative disorders. In these disorders, aggregation of disease-associated proteins disrupts nuclear pore integrity and reduces the availability of transport factors, thus impairing nuclear import and RNA export. In addition, nuclear transport plays a key role in regulating immune signalling by controlling the movement of transcription factors, such as NF-κB and STAT proteins, into the nucleus, thereby affecting inflammation, autoimmunity, and overall immune cell function. Together, these observations establish nuclear transport as a critical regulatory factor in both normal cellular functions as well as in disease conditions [5-7].

Infectious pathogens frequently exploit or perturb host nuclear transport to support their replication and evade host immune defences, as has been extensively demonstrated for viral and bacterial infections. Viral proteins commonly target nuclear transport receptors or nucleoporins to facilitate genome import. Some pathogens manipulate the host nuclear transport pathway to subvert host immune responses, prompting growing interest in nuclear transport as a therapeutic target in infectious disease [8 9]. In this article, we review our current understanding of how pathogens manipulate host nuclear transport machinery for their survival and pathogenesis. First, we briefly review a few strategies employed by viral and bacterial pathogens, as they have been extensively reviewed elsewhere [10-12]. Emerging evidence suggests that fungal pathogens also rely heavily on host nuclear transport–dependent processes, although direct manipulation of nuclear pore components has not yet been demonstrated. This review focuses on the role of nuclear transport during fungal infection, integrating insights from mammalian and plant systems and highlighting opportunities to target host nuclear transport pathways therapeutically in fungal disease.

Manipulation of nuclear transport pathways by viruses

Nucleocytoplasmic transport serves as a major "choke point" for various diseases in eukaryotes; this is primarily because NPCs are the sole gateway for molecules, including those involved in transcription and immune signalling, moving between the cytoplasm and compartmentalized nucleus. As stated above, most protein traffic across the NPC is mediated by karyopherins (importins/exportins) and RanGTP/RanGDP gradient. In contrast, bulk mRNA export is driven primarily by the NXF1–NXT1 pathway, whereas many specialized RNA/protein cargos use the CRM1/XPO1 export pathway[13]. Because these pathways determine whether the immune regulators can reach the nucleus or antiviral transcripts can reach the cytoplasm, they form an attractive control point for pathogens. For an effective antiviral defence, key transcription factors, namely STAT1/2, IRF3, and NF-kB, must enter the nucleus to induce interferon-stimulated genes. Conversely, antiviral mRNAs synthesized in the nucleus must be exported to the cytoplasm for translation [14 15]. Therefore, viruses manipulate nuclear transport through two major strategies.

First, several viruses exploit the host nuclear transport machinery to promote their own replication. They do so by accessing the nucleus for essential replication steps and utilizing the NPC components to transport viral genomes in and out of the nucleus. This strategy helps the viruses effectively hijack the host transport pathways to support their own proliferation. Second, viruses inhibit the import of immune regulators and the export of antiviral transcripts to the cytoplasm by disrupting the NPC components. This allows the pathogen to evade host immune signalling and establish a more favourable

environment for replication. Below, we briefly discuss two selected examples of how viral pathogens either exploit the nuclear transport machinery for replication or disrupt it to evade host defences.

Poliovirus (PV) disrupts nucleocytoplasmic transport largely through viral proteases, particularly 2A protease (2A pro), which cleave critical FG-nucleoporins such as Nup62, Nup98, and Nup153 [14 16]. By proteolytically remodelling NPC components, PV compromises the selective permeability of the nuclear envelope and broadly perturbs nuclear transport. A functional consequence is the mislocalization of nuclear proteins and a reduced capacity for regulated nuclear import, limiting the delivery of antiviral transcription factors to the nucleus. In parallel, PV 2A protease-induced NPC remodelling strongly impairs the nuclear export of host mRNAs, rRNAs, and U snRNAs, leading to reduced production of host antiviral proteins [17].

SARS-CoV-2 disables host nuclear transport primarily by functionally blocking the NPC rather than degrading its components. An accessory protein of Sars-Cov2, ORF6, plays a major role in compromising the nucleocytoplasmic trafficking and interferon signalling. The C-terminal tail of ORF6 contains a specific methionine residue (Met58) surrounded by acidic residues [18]. As this motif mimics the binding interface used by cellular proteins to bind the Rae1-Nup98 heterodimer, it enables ORF6 to bind the host Rae1-Nup98 complex with a significantly higher affinity than the host transport receptors. By occupying the mRNA-binding groove of Rae1, ORF6 physically blocks the "gate," obstructing the bidirectional traffic. This blocks the export of host mRNA encoding Interferon-beta, RIG-I, and IRF1, thus preventing the cell from translating the proteins needed to signal an infection to neighbouring cells. It also prevents STAT-1 and STAT-2 from docking to the pore, thereby rendering the cells less responsive to interferon signals from infected neighbours[19].

HIV-1 uses a different approach, exploiting the host nuclear transport system to deliver its large replication complex into the nucleus of non-dividing cells, such as macrophages and T cells. The HIV-1 capsid interacts directly with the FG-repeats of Nup358 and Nup153. Nup358, located on the cytoplasmic filaments of the basket, mediates the capture of the incoming capsid and positions it for entry, whereas Nup153, located on the interior side of the basket, anchors the capsid to the inner face of the pore, facilitating the final release of the viral genome near the integration-active sites of the chromatin [20]. Viral translocation into the nucleus is enabled by the viral protein Vpr, which binds to the nuclear envelope in a manner similar to importin-β, thereby aiding the entry of the viral pre-integration complex (PIC) into the nucleus. While facilitating viral import, Vpr also reshapes immune signalling by blocking the nuclear import of IRF-3 and NF-kβ, thus preventing the host from sending signals into the nucleus to activate the antiviral genes [21]. Further, the viral Rev component targets the host XPO1/CRM1, hijacking the host's primary export pathway to export the viral RNA out of the nucleus [22].

Since most viruses depend on nuclear export and import pathways during their life cycle, drugs have been developed to target these transport mechanisms specifically. Selinexor and Verdinexor inhibit the nuclear export receptor XPO1/CRM1, thereby blocking the transport of viral and host cargo proteins essential for viral replication and inflammatory signalling. In SARS-CoV-2 infection, selinexor limits viral propagation by trapping key viral proteins in the nucleus, reducing ACE2 availability at the cell surface, and dampening excessive inflammatory responses [23]. Similarly, in influenza infection, verdinexor prevents the nuclear export of viral ribonucleoprotein (vRNP) complexes, thereby suppressing viral replication while simultaneously reducing NF-kB–mediated cytokine production and immunopathology[24]. In contrast, lenacapavir targets nuclear import in HIV-1 by binding to the viral capsid and disrupting its interaction with nuclear pore components, such as NUP153 and CPSF6, thereby blocking nuclear entry and subsequent reverse transcription [25].

Manipulation of nuclear transport pathways by bacteria

While viruses frequently target the NPCs and trafficking receptors directly, bacterial pathogens mostly remodel the nucleocytoplasmic transport indirectly by secreting effector proteins that either (i) rewire transport regulators like Ran or (ii) enter the nucleus to reprogram transcription and chromatin, thereby reshaping nucleocytoplasmic trafficking without necessarily damaging the pore. We discuss two bacterial infections that exemplify these strategies.

Legionella pneumophila is an intracellular bacterial pathogen that replicates in macrophages by injecting a large repertoire of effector proteins into host cells via the Dot/Icm type IV secretion system. It disrupts the host nucleocytoplasmic network by hijacking Ran GTPase, the master regulator of the network. The MitF factor of *Legionella pneumophila* acts as a bacterial mimic of host Guanine Nucleotide Exchange Factors (GEFs), specifically the RCC1 family [26]. In a healthy cell, Ran-GTP and Ran-GDP are concentrated in the nucleus and cytoplasm, respectively. MitF disrupts this by promoting the exchange of GDP for GTP on Ran proteins in the cytoplasm. Consequently, when import receptors (Importin-β) enter the cytoplasm to bind newly synthesized cargo, the ectopic Ran-GTP generated by MitF binds to them prematurely, triggering cargo release before they reach the nuclear pore. At the same time, excessive cytoplasmic activation of Ran depletes the pool of RanGDP that must be imported back into the nucleus to sustain the Ran gradient [27].

Listeria monocytogenes secretes nucleomodulin which exploits host import pathways for its own survival. LntA secreted by these bacteria binds to BAHD1 protein, which is involved in the silencing of interferon-stimulated genes. This binding disrupts the BAHD1-associated silencing complex, leading to an increased expression of Interferon Stimulated Genes [ISGs], particularly Type III interferons, such as IFN-λ [28]. By controlling the ratio of Type I to Type III interferons, the bacterium can modulate

the inflammatory environment to favour its survival in specific tissues, such as the gut epithelium. While Type I IFN activates neutrophils, Type III IFN has been shown to inhibit their oxidative burst and migration toward the site of infection. By inducing a high Type III-to-I ratio, *Listeria* creates a "shield" against neutrophil-mediated killing. This provides a window of time for the bacteria to cross the basement membrane and reach the internal organs (liver and spleen) before a full-scale systemic immune response is mobilized.

Emerging evidence also indicates that bacteria manipulate the host nucleocytoplasmic transport network to reprogram transcriptional responses and evade immunity. Therefore, ongoing research is currently exploring host-directed therapeutic strategies that restore or stabilize nucleocytoplasmic trafficking during bacterial infection, expanding the scope of nuclear transport modulation beyond antiviral applications. Together, these findings highlight nucleocytoplasmic trafficking as a shared vulnerability across viral and bacterial pathogens and underline its importance as a versatile, evolving target for anti-infective therapy.

Manipulation of Host Nuclear Transport Pathways in Plant Fungal Infection

Higher plants recognize the immunological signals associated with pathogenic infections using both surface-level and intracellular mechanisms. Nonetheless, different types of immune responses need a tightly regulated exchange of signals between the cytoplasm and nucleus of individual plant cells. Many plant pathogens are known to alter the functions of NPCs to affect the nuclear import/export of immunity-related macromolecules in order to establish their virulence [29]. In this section, we will focus on plant fungal pathogens known to exploit nuclear transport to control the flow of plant-immunity-related molecules.

As mentioned earlier, phenylalanine glycine (FG)-rich nucleoporins constitute the central channel barrier of the NPC and mediate controlled cargo transport. Nup98, a key FG-rich nucleoporin, has been implicated in the plant immune response against fungal pathogens. Genenncher et al. have demonstrated that a MOS7/Nup 88 mutant in Arabidopsis (*Arabidopsis thaliana*) disrupts its interaction with Nup 98, thereby affecting nuclear protein export and rendering the plant more susceptible to infection with *Botrytis cinerea*, the grey mould necrotrophic fungus. The partial loss-of-function *mos7*-1 mutant used in this study was shown to be defective in activating critical pathogen-responsive mitogen-activated kinases, namely MAP3/MAP6, as well as in nuclear retention of MAP3 in Arabidopsis. The mutation did not affect *MAP3* expression but rather enhanced its nuclear export, thereby reducing its stability and weakening plant immunity against the pathogen. Further analysis showed that a four amino acid deletion (FDLS) in the N-terminal domain of *mos7*-1 rendered it incapable of efficiently interacting with Nup98a and Nup98b. Thus, the vital role of Nup98 in plant immunity, through its interaction with functional Nup88 and its effect on nuclear cargo export, was underlined in this study [30].

A more recent study has identified the essential role of another FG-rich nucleoporin, namely NUP62, which is a part of the NPC central barrier, in Arabidopsis immunity against *B. cinerea* [31]. This study showed that the expression of various defence-related genes in response to *B. cinerea* was dependent on the presence of NUP 62 and that, as compared to wild type Arabidopsis plants, *B. cinerea* propagated faster and led to more severe symptoms in *nup62* mutant plants. Plants defective in other central barrier nucleoporins, viz. NUP58 and NUP54 also showed increased infection susceptibility upon fungal invasion, indicating the critical role of the NPC central barrier in Arabidopsis against *B. cinerea* invasion. Interestingly, the authors have also shown that the NPC central barrier proteins undergo phase separation and that this mechanism is crucial for the nucleocytoplasmic transport of MPK3, which has been implicated in plant immunity against *B. cinerea*.

As observed in Arabidopsis, the rice homologue of NUP98, APIP12, was shown to be involved in immunity against *Magnaporthe oryzae*, the causal fungus of rice blast disease [32]. Notably, APIP12 is one among the 12 APIPs (AvrPiz-t interacting proteins) targeted by the AvrPiz-t effector secreted by the rice blast pathogen. APIP12 interacts with APIP6, an E3 ubiquitin ligase, and acts as a positive regulator of the basal resistance of rice plants to blast disease. APIP6 is required for pathogen-associated molecular pattern-triggered plant immunity; AvrPiz-t can suppress its E3 ligase activity, thereby suppressing the plant immune response. Knocking down or knocking out of APIP12 resulted in an increased susceptibility of rice plants to *M. oryzae*. In addition, mutation in Arabidopsis lamin homolog LITTLE NUCLEI/CROWDED NUCLEI (LINC/CRWN), LINC1, has been implicated in increased plant resistance toward *B. cinerea*. The *linc1* mutant exhibited enhanced resistance to fungal infection, attributed to a substantial increase in the expression of jasmonic acid (JA) response genes in this mutant [33]. Further, nuclear transport receptors are also implicated in plant immunity. An example is KA120, a nuclear transport receptor in Arabidopsis; the *ka120* mutant showed resistance to the powdery mildew pathogenic fungus *Golovinomyces cichoracearum* [34].

Pathogenic fungi can also evade plant immunity by secreting effectors; intracellular effectors can either localize to plant cell cytoplasm or the nucleus. Herein, we will briefly discuss the nuclear effectors secreted by plant pathogenic fungi. Most of these pathogenic fungal effectors contain a specific nuclear localization sequence (NLS), which they exploit to gain entry into the host plant nucleus. For example, MoHTR1 is a nuclear effector secreted by *M. oryzae*. This effector contains a specific NLS (with RxKK being the core region) and gains an entry into rice nuclei by virtue of its interaction with importin α [35]. On the other hand, another *M. oryzae* nuclear effector, viz. MoHTR2 enters the host nucleus via the non-classical pathway, i.e., it does not interact with any of the rice importin αs or importin βs. A recent study has identified ^{53}HH^{54} as an essential part of the likely NLS region, comprising amino acids 49-63 at the N terminus of MoHTR2; this stretch, which contains two histidine residues, was shown to be essential for importin-independent

nuclear localization of MoHTR2 in rice [36]. Another mechanism exploited by the fungal nuclear effectors to enter plant nuclei is their binding to specific plant proteins with NLS. For example, *Fusarium oxysporum* f. sp. *lycopersici* (*Fol*), the causative agent of *Fusarium* wilt in tomato, secretes an effector named *Fol*-Secreted Virulence-related Protein1 (FolSvp1) into the apoplast. Here, FolSvp1 binds tomato protein SIPR1, which contains a specific NLS, and then translocates along with it to the nucleus. The fungal effector thus hitchhikes the plant machinery for its own nuclear localization [37].

Once plant pathogenic fungal effectors enter the host nucleus, they can modulate plant immunity and establish infection in many ways. For example, *the M. oryzae* effectors MoHTR1 and MoHTR2 are known to reprogram transcription of several immunity-related genes in rice. These effectors specifically bind to the 'effector binding element' in the promoter region of target genes in host nuclei, thereby repressing their transcription and suppressing the plant defence system [38]. A few effectors also bind transcription factors, altering their nuclear localization and thereby affecting the plant immune response. For example, *Puccinia striiformis* f. sp. *tritici* (*Pst*), which causes stripe rust in wheat, secretes a glycine-serine-rich effector protein PstGSRE1. This effector binds to transcription factor TaLOL2 and disrupts its nuclear localization. This inhibits TaLOL2-induced ROS-mediated cell death, thereby weakening host immunity [39]. In addition, fungal effectors can also exploit trans-kingdom antifungal RNAi-mediated plant immunity to establish virulence. *Verticillium dahliae*, the causative agent of wilt disease, secretes effector VdSSR1 (Secretory Silencing Repressor 1) in host plant cells. VdSSR1 localizes to the nucleus, wherein it sequesters ALY family proteins, which are essential adaptors of the TREX (Transcription-Export) mRNA transport complex. This attenuates nuclear export of the AGO1–microRNA (AGO1–miRNA) complex, thus reducing the levels of antifungal miRNAs in fungal cells and increasing fungal virulence [40]. Another study has shown that fungal effectors can also evade phase-separation-mediated plant immunity. Wang et al. have recently demonstrated that BcSSp2, a nuclear effector secreted by *B. cinerea*, can disrupt the phase separation of NUP62 at the central barrier of the NPC and attenuate phase-separation-based nuclear transport of MPK3, a key immune regulator in Arabidopsis; this strategy helps this necrotrophic fungus facilitate infection [41]. A detailed review regarding different types of nuclear effectors secreted by plant pathogenic fungi has been published earlier[42]. For an overview of various nuclear effectors secreted by different types of plant pathogens, readers can refer to Harris et al., 2023 [43].

Manipulation of Host Nuclear Transport Pathways in Mammalian Fungal Infection

Fungal diseases affect more than one billion people worldwide each year. They are estimated to contribute to approximately 3.8 million deaths annually, reflecting both direct and indirect mortality associated with invasive fungal infections. A substantial proportion of this mortality is due to a limited number of pathogens, including *Aspergillus spp.* (approximately 300,000–600,000 deaths per year), *Cryptococcus neoformans* (180,000–200,000 deaths per year), *Candida spp.* (300,000–400,000 deaths per year), and *Pneumocystis jirovecii* (200,000–400,000 deaths per year)[44] [45]. These pathogenic fungi have developed diverse strategies to invade mammalian hosts and establish infection, affecting the host at both physiological and cellular levels. Compared with viral and bacterial pathogens, fungal pathogens have received less attention at the molecular and mechanistic levels of host–pathogen interactions. Herein, we focus on one such underexplored aspect of fungal infection in mammalian systems, highlighting existing knowledge gaps and outlining potential directions for future research.

Early host defence against fungal infections is initiated by pattern-recognition receptors that activate conserved innate immune signalling pathways. Some of these pathways include NF-kB and MAPK signalling, which rely on efficient nucleocytoplasmic transport to rapidly reprogram transcription in mammalian host cells rapidly [46] [47]. To counteract this acute host immune response, many pathogens have evolved strategies to interfere with host defence mechanisms, including modulation of innate immune signalling pathways [48]. These pathways, therefore, represent critical regulatory points and attractive targets for therapies. Given that the activation of key transcription factors depends on tightly regulated nucleocytoplasmic transport, perturbation of this process may represent an underappreciated mechanism by which fungal pathogens influence host defence.

Infection by *Candida albicans* (Candida) elicits a multilayered host response that is dependent on regulated nucleocytoplasmic transport. Host recognition of *Candida* cell wall components and hypha-associated factors activates conserved innate immune signalling pathways, including NF-kB and MAPK signalling, which rely on repeated and tightly controlled nuclear translocation of transcription factors to initiate and sustain inflammatory and antimicrobial gene expression [49] [50]. A central driver of this response is candidalysin, a hyphal-associated peptide toxin that induces calcium influx and membrane stress in epithelial cells, thereby triggering EGFR–MAPK and NF-kB signalling cascades that culminate in rapid transcriptional reprogramming within the nucleus [51] [52]. Beyond candidalysin-mediated signalling, *Candida* infection is characterized by prolonged and dynamic nuclear shuttling of transcription factors associated with innate immunity, stress responses, and cell survival, suggesting that the kinetics and capacity of nuclear import and export processes may critically shape host outcomes. In phagocytic cells, *Candida* can survive intracellularly and drive extensive host transcriptional and metabolic reprogramming, processes that inherently depend on regulated nuclear trafficking of immune regulators, metabolic sensors, and chromatin-associated factors [53] [54]. Hyphal growth and host cell deformation during infection may further impose mechanical stress on the nucleus, a condition known in other systems to influence nuclear envelope integrity and nuclear pore permeability, thereby potentially modulating transport dynamics during infection. In addition, *Candida* infection has been shown to induce

epigenetic and chromatin-level reprogramming of host cells, including features of trained innate immunity, implying sustained nuclear import of chromatin-modifying enzymes and transcriptional regulators over prolonged periods [55-57]. Collectively, these findings indicate that although *Candida* does not directly target nuclear pore complexes or transport receptors, multiple facets of *Candida* pathogenesis converge on host defence pathways that are critically dependent on nucleocytoplasmic transport, highlighting nuclear transport as a critical point and an underexplored layer of host–pathogen interaction during fungal infection.

Cryptococcus neoformans is another prime example of a mammalian fungal pathogen in which nucleocytoplasmic transport of immune effectors in host cells plays an important role in host defence. *Cryptococcus* can survive the acidic environment of phagolysosomes, multiply, and later escape macrophages without killing them [58 59]. Recognition of Cryptococcus by host pattern-recognition receptors activates innate immune pathways that converge on nuclear transcriptional programs, including NF-kB, MAPK, and STAT signalling cascades, all of which require tightly regulated nuclear import and export of transcription factors. In particular, Cryptococcus infection strongly engages cytokine-driven JAK–STAT pathways, with STAT1 and STAT3 activation playing central but opposing roles in antifungal immunity, macrophage polarization, and disease outcome [60 61]. Protective host responses are associated with STAT1-dependent classical macrophage activation and transcriptional programs that promote fungal clearance, whereas STAT3 activation is linked to alternative macrophage activation, immune suppression, and fungal persistence, underscoring the importance of nuclear STAT trafficking dynamics in forming host defence. Beyond cytokine-driven STAT activation, intracellular *Cryptococcus* induces extensive host transcriptional reprogramming, including modulation of stress responses, metabolic pathways, and immune regulatory networks, processes that inherently depend on sustained nucleocytoplasmic transport of transcription factors, chromatin regulators, and metabolic sensors [62 63].

Recent proteomic and cell biology studies further demonstrate that *Cryptococcus* releases fungal proteins during intracellular residence within macrophages, providing a potential route by which fungal-derived factors may influence host nuclear signalling either directly or indirectly [64 65]. In addition, *Cryptococcus* possesses a prominent polysaccharide capsule that slows down host immune activation and alters cytokine environments, thereby indirectly reshaping STAT-dependent nuclear transcriptional responses. The ability of *Cryptococcus* to undergo non-lytic exocytosis and repeated cycles of phagocytosis further exposes host cells to fluctuating immune signals, necessitating dynamic, and repeated nuclear trafficking of immune regulators over the course of infection [58 66]. Collectively, these observations indicate that while direct targeting of nuclear pore complexes or transport receptors by *Cryptococcus* has not been demonstrated, multiple hallmarks of cryptococcal pathogenesis—including intracellular survival, cytokine-mediated STAT signalling, immune polarization, and host transcriptional reprogramming—converge on pathways that are critically dependent on regulated nucleocytoplasmic transport. This positions nuclear transport as a central yet underexplored determinant of host–*Cryptococcus* interactions and disease outcome.

Collectively, these observations establish that host nucleocytoplasmic transport is a central determinant of antifungal immunity, governing the activation and regulation of key transcriptional programs during infection. In the context of *Candida albicans* and *Cryptococcus neoformans*, modulation of nuclear transport-dependent pathways emerges as a critical interface between host defence and pathogen survival. The following table summarises other representative pathogens, along with these fungi, in which host nucleocytoplasmic transport pathways are modulated to circumvent infection.

Table 1: List of fungal pathogens affecting mammals, along with the role of host nuclear transport during infection

Name of the fungal pathogen	Disease caused	Involvement of host nuclear transport	References
Candida albicans	Candidiasis	Host recognition of Candida cell wall components and hypha-associated factors activates conserved innate immune signalling pathways, including NF-kB and MAPK signalling, which rely on repeated and tightly controlled nuclear translocation of transcription factors to initiate and sustain inflammatory and antimicrobial gene expression.	49 52
Cryptococcus neoformans	Cryptococcosis	Recognition of Cryptococcus by host pattern-recognition receptors activates innate immune pathways that converge on nuclear transcriptional programs, including NF-kB, MAPK, and STAT signalling cascades, all of which require tightly regulated nuclear import and export of transcription factors	60-63
Aspergillus fumigatus	Invasive aspergillosis	Immune signaling activates transcription factors like NF-kB, NFAT, and STATs, which are transported into the nucleus via importins to drive antifungal gene expression.	67 68 69

Name of the fungal pathogen	Disease caused	Involvement of host nuclear transport	References
Pneumocystis jirovecii	Pneumocystis pneumonia	Nuclear transport of STAT1, NF-kB, and NFAT is central to coordinating macrophage and T-cell responses, and defects in these pathways strongly correlate with disease severity rather than just pathogen load.	70 71
Histoplasma capsulatum	Histoplasmosis	Immune control of *Histoplasma* depends heavily on STAT1 and NF-kB nuclear import, while the pathogen actively suppresses or skews nuclear translocation to survive inside macrophages.	72 73

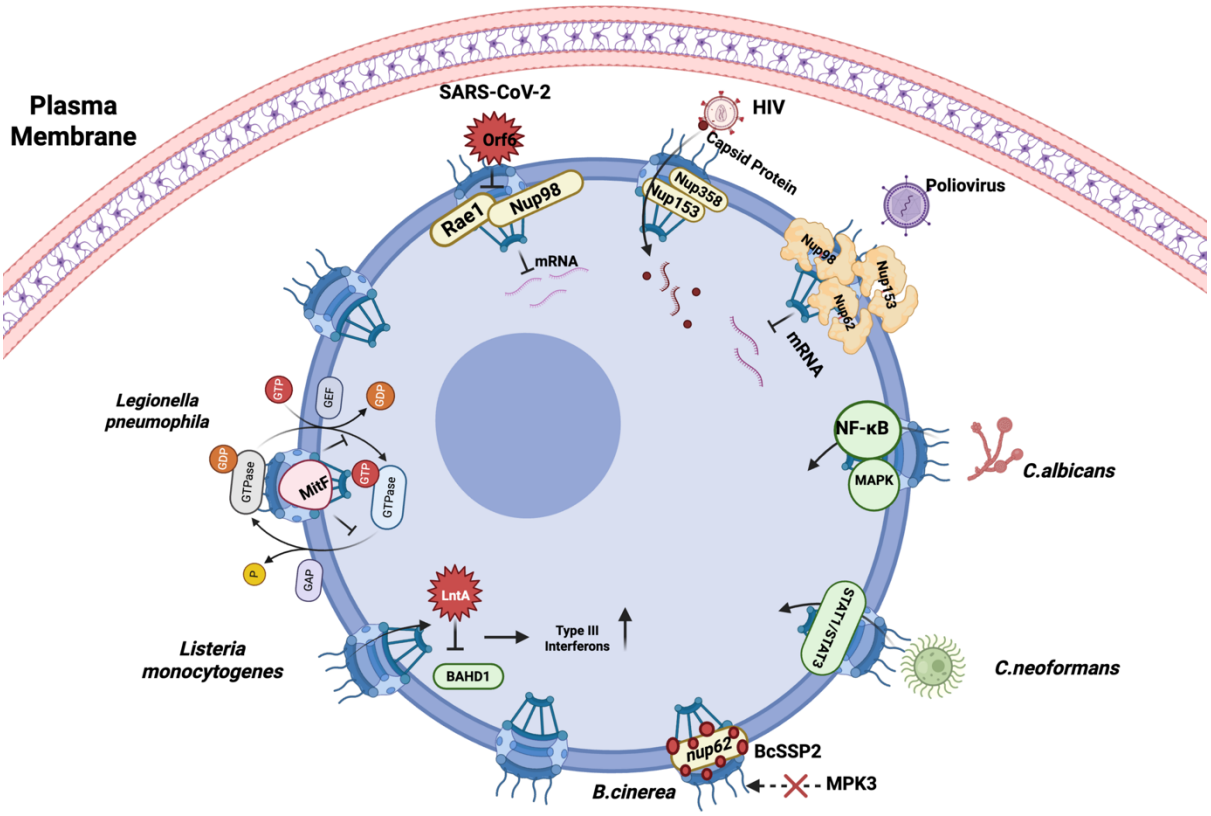

Figure 1: Pathogen-mediated modulation of nucleocytoplasmic transport.
Schematic overview illustrating how diverse pathogens target the nuclear pore complex (NPC) and nucleocytoplasmic trafficking. SARS-CoV-2 ORF6 interacts with the Rae1–Nup98 complex to block host mRNA export and inhibit nuclear import of immune transcription factors. HIV-1 utilizes Nup358 and Nup153 to facilitate docking and nuclear entry of the viral capsid. Poliovirus protease-mediated cleavage of FG-NUPs (including Nup62, Nup98, and Nup153) disrupts the permeability barrier, impairing nuclear import and host RNA export. Bacterial pathogens primarily perturb transport regulation rather than NPC structure. *Legionella pneumophila* secretes effectors that mimic Ran guanine nucleotide exchange factors (RanGEFs), disrupting the RanGTP/RanGDP gradient and causing loss of directionality in nuclear transport and premature cargo release. *Listeria monocytogenes* exploits host importin-dependent pathways to translocate bacterial effectors into the nucleus, leading to reprogramming of host transcriptional responses, including type I interferon signalling. Plant fungal pathogens target both NPC components and transport pathways. Botrytis cinerea effector BcSSP2 interferes with Nup62-mediated phase separation, impairing selective transport of MPK3 through the pore. Mammalian fungal pathogens such as *Candida albicans* and *Cryptococcus neoformans* rely on intact host nucleocytoplasmic transport for immune signalling, with pathogenic outcomes shaped by the nuclear trafficking of key host transcription factors, including NF-kB, MAPKs, and STAT1/STAT3.

Conclusions

The absence of direct evidence for fungal manipulation of nucleoporins should be viewed as a significant gap in current knowledge rather than evidence of irrelevance. As outlined earlier, mammalian viruses target specific nucleoporins in the host nucleus, whereas bacterial pathogens exploit nucleocytoplasmic transport to establish infection. However, whether the fungal pathogens alter host nucleoporins and/or nucleocytoplasmic transport remains largely unknown. Future studies designed to directly interrogate nuclear transport during fungal infection—using live-cell nuclear import and export reporters, high-resolution imaging of nuclear pore integrity, proximity-based proteomics to identify pathogen-induced alterations in transport machinery, and targeted genetic or pharmacological

perturbation of importin–exportin pathways—will be essential to determine whether and how fungal pathogens exploit this process. Such approaches may ultimately reveal nuclear transport as a novel host-directed therapeutic target for the treatment of invasive fungal diseases. However, since both the NPC structure and nuclear transport pathways are highly conserved between fungi and mammals, targeting this pathway can be challenging. For example, an Xpo1 inhibitor, viz. Leptomycin B was initially identified as a fungal growth inhibitor, but was not advanced beyond the preclinical stage due to severe toxicity in humans. Nonetheless, future studies could focus on identifying such fungal proteins, if any, that are imported into the host nucleus for establishing successful infection. This should be followed by identifying key differences or specific interactions that prevent the entry of such fungal proteins into host cells, which could then be exploited as effective therapeutic targets.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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