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Fantastic nuclear envelope herniations and where to find them

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Abstract

Morphological abnormalities of the bounding membranes of the nucleus have long been associated with human diseases from cancer to premature aging to neurodegeneration. Studies over the past few decades support that there are both cell intrinsic and extrinsic factors (e.g. mechanical force) that can lead to nuclear envelope “herniations”, a broad catch-all term that reveals little about the underlying molecular mechanisms that contribute to these morphological defects. While there are many genetic perturbations that could ultimately change nuclear shape, here, we focus on a subset of nuclear envelope herniations that likely arise as a consequence of disrupting physiological nuclear membrane remodeling pathways required to maintain nuclear envelope homeostasis. For example, stalling of the interphase nuclear pore complex (NPC) biogenesis pathway and/or triggering of NPC quality control mechanisms can lead to herniations in budding yeast, which are remarkably similar to those observed in human disease models of early-onset dystonia. By also examining the provenance of nuclear envelope herniations associated with emerging nuclear autophagy and nuclear egress pathways, we will provide a framework to help understand the molecular pathways that contribute to nuclear deformation.

Keywords

Nuclear envelope; nuclear pore complex; herniation; ESCRT; Torsin; nucleophagy; nuclear egress

Introduction

Alterations to the shape of the nucleus is a hallmark pathognomonic cellular feature of many human diseases, but it is often challenging to determine the underlying causality of these abnormalities and whether they ultimately directly contribute to disease progression[1,2]. Such is the case with the majority of examples where nuclear envelope (NE) protrusions or “herniations” have been observed extending into the cytosol. As these herniations show a continuum of size (from nano to microscale), they are challenging to categorize by morphology alone and could thus benefit from a greater understanding of the underlying molecular mechanisms that cause them. Interestingly, recent work has helped to define how physiological nuclear membrane remodeling might, when perturbed, contribute to the biogenesis of some NE herniations; they are providing a retrospective framework to help interpret the many herniations observed over the past few decades in diverse model systems. Here, we will focus on the studies that primarily explore herniations visible at the nanoscale

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(see Table 1) while also touching on those visible by light microscopy (often also termed NE "blebbing" or "ruffling") observed in other contexts and more comprehensively covered elsewhere [2–5].

The nuclear envelope

The NE is contiguous with the endoplasmic reticulum (ER) and thus surrounds the genome in two biochemically distinct membranes, the outer and inner nuclear membrane (ONM and INM); the ONM and INM are separated by the perinuclear space (PNS; Figure 1). While the ONM is generally considered to be near-compositionally identical to the ER (with some exceptions, e.g. KASH-domain proteins[6]), the INM has a unique complement of integral and peripheral membrane-associated proteins that directly interface with the genome[6]. The most well described of these are the nuclear lamins, that while absent from yeasts, form a filamentous scaffold that provides mechanical support to the nucleus and helps maintain its integrity[5].

Molecular traffic across the NE is controlled by nuclear pore complexes (NPCs), ~100 MD protein channels in Metazoans (~50 MD in budding yeast) that are formed by concentric inner, outer and membrane ring assemblies that scaffold a central transport channel, cytosolic filaments and nuclear basket (Figure 1)[7,8]. These architectural units are themselves constructed from modular subcomplexes of proteins termed nucleoporins or nups that are assembled step-wise into the NE, with an emerging role for unstructured motifs that connect subcomplexes together to help build the NPC[8–10]. There remains considerable interest in understanding the biochemical and morphological differences that define post-mitotic and interphase modes of NPC assembly[11–13]. Of note, recent evidence supports that post-mitotic NPC assembly begins within small (<50 nm) pores in the reforming NE, whereas interphase NPC assembly requires an INM-ONM fusion event[12,13]. Interestingly, the molecular fusogen that drives INM-ONM fusion has eluded genetic (or biochemical) identification. Identifying the fusion mechanism is a priority as it is becoming clear that some NE herniations likely arise due to defects in NPC biogenesis, and/or, surveillance mechanisms that seal off defective NPCs[14,15].

Blockade of early interphase NPC biogenesis steps

A commonly observed ultrastructural feature of the NE are small INM evaginations with a base diameter of ~40–60 nm that do not impact ONM morphology[16–23](Figure 2A, B, Table 1, blue rows).Thus, these structures fall short of "herniating" the NE, but they are likely progenitors to the more elaborate NE herniations described below. In virtually all cases where these structures have been observed, they are associated with genetic perturbation of genes encoding components of the NPC[16], NPC assembly factors[17,19], or the soluble nuclear transport apparatus including nuclear transport receptors[21,22] and the Ran GTPase[23]. This has led to the concept that these evaginations are stalled biochemical/structural intermediates in early NPC assembly. Consistent with this idea, conditional depletion of the inner ring nup gene, *NUP170* in a genetic background where its paralogue *NUP157* is also deleted, leads to the INM-accumulation of a distinct set of nups including components of the nuclear basket[16]. These data, in addition to other genetic and biochemical links between the INM and specific nup genes[24–29], support that key

assembly events occur at the INM. Indeed, the collation of EM tomograms into a morphological timeline of interphase NPC assembly is consistent with the idea that assembly proceeds inside-out with the earliest discernable morphological feature being INM evaginations[12](Figure 2A).

Blockade in late interphase NPC assembly

It is likely that these small INM-evaginations can also lead to a much larger NE herniation where one can discern a neck at the INM of ~80–100 nm, often with considerable electron density enclosed within the protrusion (Figure 2B). While such a structure is not visible during “normal” NPC biogenesis, it is likely that it too is caused by a delay or abrogation of NPC assembly, but at a later step than the small INM evaginations that precede it (Table 1, teal rows). Indeed, as NPC assembly progresses, a “mushroom” like density appears to evaginate the INM before its fusion with the ONM[12](Figure 2A). These events likely coincide with the recruitment of additional nup subcomplexes capable of forming an 8-fold radially-symmetric structure (likely the nucleoplasmic outer ring), which can be visualized in *en face* sections of the INM[12]. Moreover, at least a subset of Phe-Gly (FG) repeat rich nups, the key proteins that establish the diffusion barrier and transport selectivity of NPCs, are also assembled before INM-ONM fusion. These observations, in the context of several other studies[19,24,30–34], have contributed to a rough ordering of nup subcomplex recruitment to a nascent NPC assembly site, with a key transition point occurring at or just after INM-ONM fusion. At this critical step, the cytosolic-facing mRNA export platform is assembled alongside other cytosolic-facing nups like Nup358, which anchors two concentric outer ring “Y-complexes” together on the cytosolic side of the NPC (at least in Metazoans[35], budding yeast only have one Y-complex ring and lack Nup358[8,36]), effectively completing NPC assembly. We suggest that genetic perturbations that prevent INM-ONM fusion lead to the formation of NE herniations (Figure 2B).

Consistent with the idea that NE herniations might arise due to a blockage of late steps in NPC assembly, they have been observed upon perturbation of several scaffold nups in yeast[37–49] and in flys[50]. In addition, due to the lack of assembly of the mRNA export platform, these alleles are often associated with an mRNA export block. For example, in budding yeast, this includes knockouts or conditional alleles of *GLE2*[51], *NUP116*[52–54] and its paralogues[46,55,56] but also extends to proteins that impact lipid homeostasis[57,58] including a membrane protein that alters membrane fluidity encoded by *APQ12*[59–61](first identified in a screen to uncover mRNA-export mechanisms[62]).

Interestingly, morphologically analogous herniations have also been observed in human[63], mouse[64–68], worm[69], and fly[60] cells upon disruption of the function of the ER-lumenal AAA+ ATPase Torsin A and its membrane-spanning co-factors LAP1 and LULL1[63]. Recent high resolution EM tomography studies of Torsin knockout HeLa cells further supports the conclusion that these herniations arise due to a disruption in NPC assembly, as their bases have NPC-like structures[63]. In addition, similar to the yeast counterparts, the cytosolic-facing nup, Nup358, might not be properly assembled[71]. A key challenge going forward will be to define the mechanism of Torsin A function in NPC biogenesis as it will also inform how an in-frame deletion of a glutamate residue in the

Torsin A gene causes early onset dystonia[72]. But, as it is absent from yeasts, it is most likely that Torsin A plays an indirect role in NPC assembly, perhaps by controlling access of a yet-to-be defined fusogen to a nascent pore assembly site. In yeast, such a role could be performed by the essential integral NE proteins Brl1 and Brr6, which localize at INM evaginations and physically interact with nups[73]. Consistent with the interpretation that they are required for NPC assembly, NE herniations build up in the absence Brr6[60,74] or Brl1/Brr6 function[73]. While it remains to be determined how Brl1 or Brr6 contribute to INM-ONM fusion, it is remarkable that overexpression of *BRL1* prevents the formation of herniations (or perhaps drives their resolution) in *nup116Δ* strains[73].

Taken together, the consistency in the appearance of morphologically similar NE herniations from yeast to human suggests that the INM-ONM fusion step during interphase NPC assembly is susceptible to perturbation and could be under control of regulatory mechanisms that might (for example) trigger fusion at a point where the nascent NPC is “ready” to receive cytosolic-facing components (fusion/surveillance checkpoint, see Figure 2C). Consistent with this idea, disruption of newly discovered interactions between the FG-repeats (of the GLFG-type) that fill the central transport channel and key scaffold nups, like Nup188, play important roles in NPC biogenesis, perhaps by helping to glue the scaffold together; conditional disruption of these interactions leads to herniations[41]. As the GLFG nups also play important roles in establishing the NPC diffusion barrier[75–77], it makes considerable sense to couple their assembly to the NPC scaffold to ensure that once INM-ONM fusion occurs, there will be no concomitant loss of nuclear-cytosolic compartmentalization.

Triggering NPC quality control

But what are the consequences if INM-ONM fusion occurs prematurely, or, if an existing NPC loses key components due to degradation because of oxidative (or other) damage? For example, while the NPC scaffold is extremely long lived, particularly in post-mitotic cells like neurons[78–80], the GLFG-rich Nup116 is lost from replicatively-old NPCs in budding yeast[81,82]. This observation is telling as *nup116Δ* NPCs have also been shown to acquire double-membrane seals after a shift to a non-permissive growth temperature resulting in morphologically-identical herniations as those associated with defective NPC assembly[52]. Thus, loss of function of Nup116 results in herniations that could arise either due to a lack of INM-ONM fusion, or, through surveillance mechanisms that seal off defective NPCs and/or NPC assembly intermediates[52] (Figure 2C, D).

A mechanism for how cells could re-seal a nuclear pore formed through premature INM-ONM fusion, or, one capable of sealing off a defective NPC likely requires the function of the endosomal complexes required for transport (ESCRT). This assertion is based on our work demonstrating the NE recruitment of the ESCRT component Chm7 (the yeast orthologue of CHMP7) by the integral INM protein Heh1 (the orthologue of human LEM2) under conditions in which NPC assembly is blocked[15]; Chm7 recruitment is most striking in *nup116Δ* and *apq12Δ* cells, strongly correlating NE herniations with Chm7 function. Moreover, the viability and the maintenance of nuclear-cytosolic compartmentalization of *nup116Δ*[15] and *apq12Δ*[83] cells requires *CHM7*. A role for the ESCRT machinery in

NPC quality control is attractive as they are well established to form spiraling polymers capable of stitching membranes together at multiple subcellular locations[84]. In this way, they might also help seal the NE at the end of mitosis, or after NE rupture events[85–88]. Indeed, ESCRTs are emerging as a key molecular machinery that surveils the integrity of many membrane-bound compartments including endo-lysosomes[89].

In all of these scenarios, the precise mechanism of Chm7 and downstream ESCRT components like Snf7 (CHMP4 in humans), function at the NE remains ill defined. Specifically, while one can imagine a mechanism in which Chm7 counteracts premature INM-ONM fusion by, for example, re-sealing a small (<100 nm diameter) hole (Figure 2C), it is more challenging to contemplate how an existing defective NPC is sealed over, which would likely require local membrane remodeling to expand the pore membrane (Figure 2D). Likewise, how a large (>100 nm diameter) NE rupture could be repaired solely by the ESCRT machinery is also difficult to imagine. An attractive model for both of these examples, however, might be the local delivery and NE-incorporation of ER-membrane sheets, in analogy to how *Drosophila* embryos expand their NE during rapid early cell divisions[90].

Herniations associated with nuclear egress and nucleophagy

Interestingly, NE herniations that are morphologically similar to those associated with NPC biogenesis have also been observed as intermediates in pathways of nuclear egress. For example, herpesvirus exits the nucleus by budding through the NE lumen/PNS[91,92] (Figure 3). While the molecular machinery that drives herpesvirus egress is encoded by the viral genome (the nuclear egress complex/NEC) and is thus distinct from NPC biogenesis, there is nonetheless evidence for the involvement of ESCRTs[93,94] and Torsin A[95] (and LULL1[96]) in the viral lifecycle hinting at a functional relationship with host nuclear membrane remodeling pathways. Further, Torsin A has been implicated in an egress pathway for so-called “Mega” RNPs that functions in the cells of *Drosophila* neuromuscular junctions[70,97] and in sea urchin embryos[98]. A key challenge, however, will be to distinguish if the NE herniations observed in these cells are functionally distinct from those linked with NPC biogenesis in mammalian cell culture[63]. Regardless, the concept that proteins/RNAs might exit the nucleus through a vesicular intermediate remains attractive and has been hypothesized to function as a clearance mechanism for nuclear aggregates[99]. While there is no direct evidence to yet support this idea, such a pathway could be used to remove defective NPC assembly intermediates from the INM[14,100]; interestingly, K48-linked ubiquitin can be found concentrated within the herniations of Torsin knockout cell lines[63](Figure 2B–D), but the identity of the ubiquitylated proteins remains unknown.

That herniations of the NE could be associated with quality control pathways that clear defective components from the INM and/or nucleus can also be gleaned from work on nuclear autophagy or “nucleophagy” pathways. For example, NE herniations can be visualized in the vacuoles of budding yeast as an intermediate in piece meal microautophagy of the nucleus (PMN)[101].The mechanisms that drive herniation formation remain ill-defined, but clearly depend on direct connections between the vacuole membrane and the ONM[101] that likely also extend to the INM[102]. While a direct analog of this pathway

has yet to be discovered in mammalian systems, it is not coincidental that the clearance of Lamin B1 (observed upon overexpression of an oncogenic HRasV12 protein) in mammalian cell culture might also proceed through a NE herniation intermediate[103]. Likewise, the overexpression of an Epstein virus protein, BFRF1 might trigger a nucleophagy-type pathway that incorporates the resolution of a NE herniation into a cytosolic vesicle targeted by the autophagy pathway[104]. It remains conceptually challenging, however, to contemplate the molecular mechanisms behind how a NE herniation could be pinched off from the nucleus while maintaining nuclear integrity, let alone how it engages the autophagy machinery.

Mechanically-induced NE herniations

While a nucleophagy mechanism would likely require maintenance of NE integrity, there are many other NE herniations that can lead to NE rupture. These herniations are sufficiently large that they can be visualized by light microscopy and might contribute to the often dramatic nuclear deformations that have been associated with cancers and other human diseases, including the laminopathies (extensively reviewed elsewhere[2,4,105]). While the provenance of these herniations are not always understood, there is evidence to support that at least a subset might be caused by direct mechanical force imposed by extrinsic environmental factors. For example, during cell migration through constrictions that are smaller than the nucleus, herniations of the NE arise and often lead to NE rupture[86,87]. These herniations are also often associated with a break or discontinuity within the lamin network that underlies the INM[86,87,106,107].

Herniations associated with mechanical strain on the nucleus have also been observed in cell culture, primarily of cancer cells[106–109]. In this scenario, mechanical force that drives herniation growth is likely also imposed by nuclear confinement, but in this case through the perinuclear actin network that could directly connect to the NE through the linker of nucleoskeleton and cytoskeleton (LINC) complexes, which directly connect the cytoskeleton to nuclear factors through a translumenal bridge[109]. As is with the case of NE herniations caused by cell migration through constrictions, these herniations are chromatin-filled and occur at sites of lamina discontinuity[107,109,110]. It remains enigmatic how mechanical force is translated into the formation of a herniation but it is clear that this process is directly impacted by extracellular cues some of which trigger elaborate feedback mechanisms that modulate the output of both nuclear and cytosolic cytoskeletons[3,111–113]. It is likely that a combination of misregulation of these feedback mechanisms with defects in the mechanical networks themselves (e.g. the lamina) increase the propensity of NE herniations *in vivo* and might directly contribute to disease mechanisms.

Outlook

While we have focused on NE herniations that, by their very definition, protrude outward from the nucleus, there are also interesting intranuclear membrane intrusions[114] that might contribute to forming the “nucleoplasmic reticulum”[115]. Like the herniations discussed here, the nucleoplasmic reticulum has also been associated with pathology, even as it is likely a product of physiological processes that remain to be fully understood. Thus, a key challenge for the future is to identify the molecular mechanisms driving specific nuclear

membrane remodeling events that can lead to often remarkable morphological changes to the NE. The introduction of membrane-remodeling proteins[17,19] and ATP-utilizing machineries[14,63,116] to the NE is clearly a step in this direction, however, it might be that their local regulation is the most important factor for defining whether membrane remodeling is productive or not. Once these regulatory processes are understood, perhaps there is a chance to define how they might contribute to disease.

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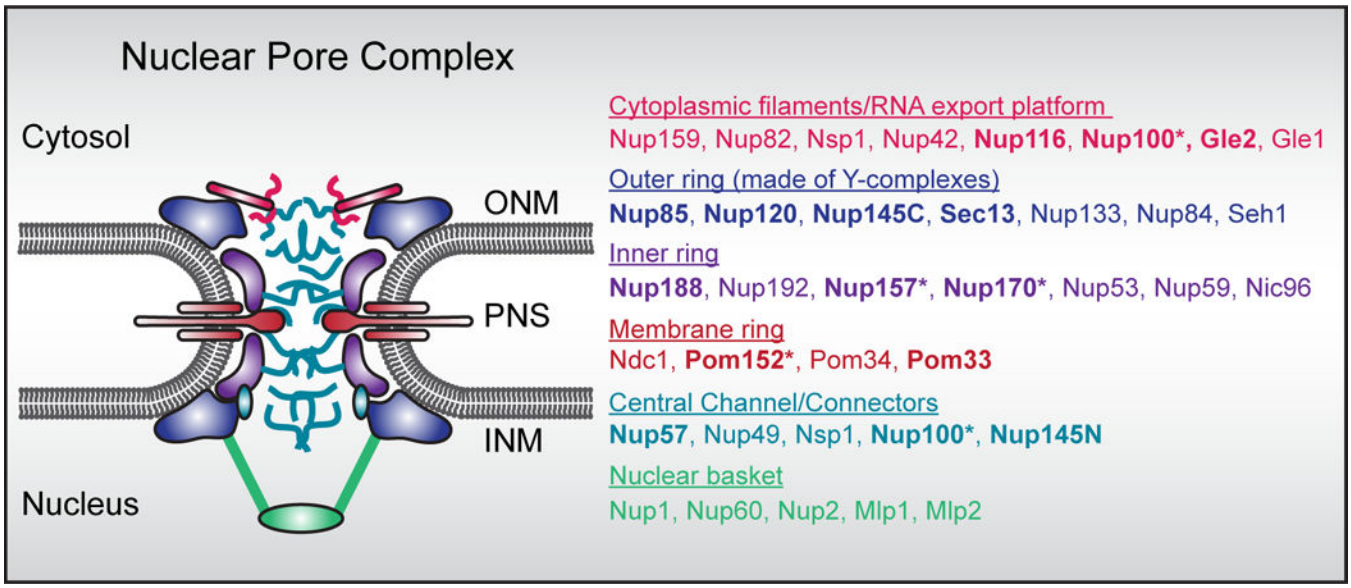

Figure 1.

A. Schematic of the nuclear pore complex with color coded nup subcomplexes. Only budding yeast nup names are listed. Loss of function of bolded nups are associated with NE herniations either alone or upon loss of function of an additional gene (indicated by *). Also see Table 1.

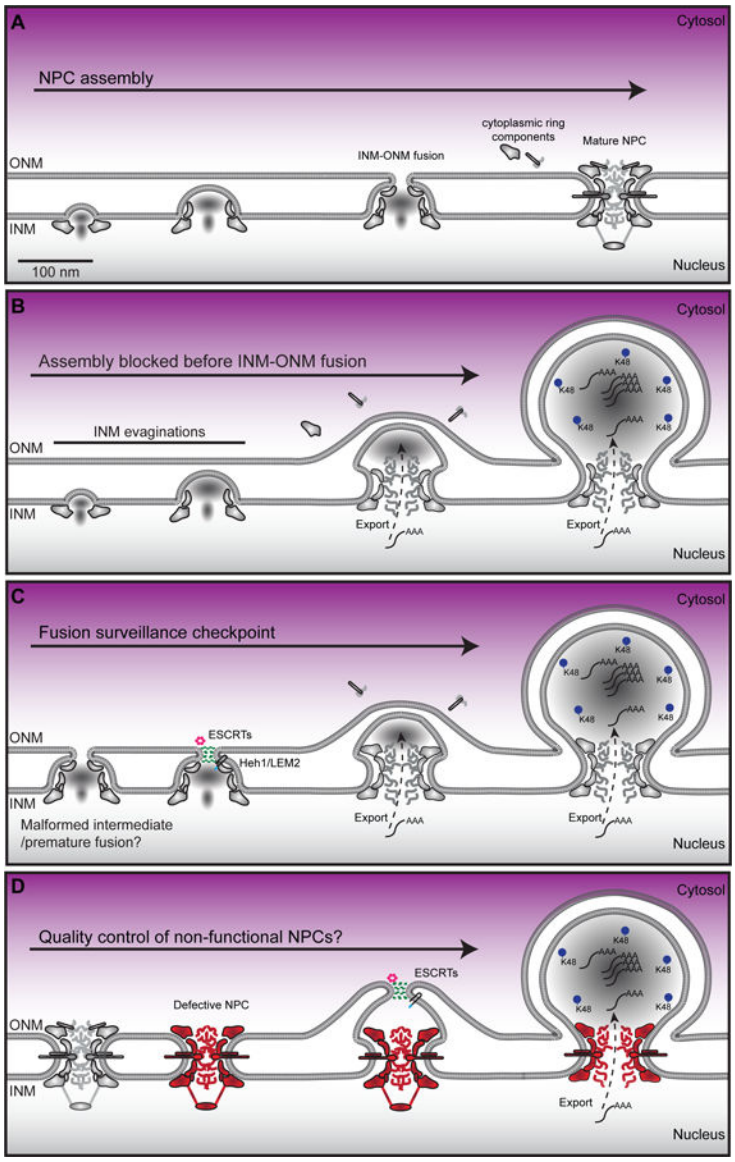

Figure 2.

Potential mechanisms that lead to NE herniations associated with NPC biogenesis and/or quality control. A. *De novo* interphase NPC assembly begins by recruitment of nups to the INM followed by INM evagination. As assembly progresses fusion occurs between the INM and ONM, which is followed by the assembly of the cytosolic filaments/mRNA export platform. B. Model of herniation formation due to a block in NPC assembly before INM-ONM fusion. Poly-A (AAA) RNA has been found in herniations as has K48-linked ubiquitin. C. Model of herniation formation due to NPC assembly surveillance by the ESCRT complex (green) and the AAA ATPase Vps4 (pink) recruited by Heh1/LEM2. D. Model of herniation formation due to loss of function (e.g. oxidative damage to NPCs/ degradation of nups) of NPCs. Note this model would require expansion of the pore membrane before sealing by the ESCRT (or other?) pathway.

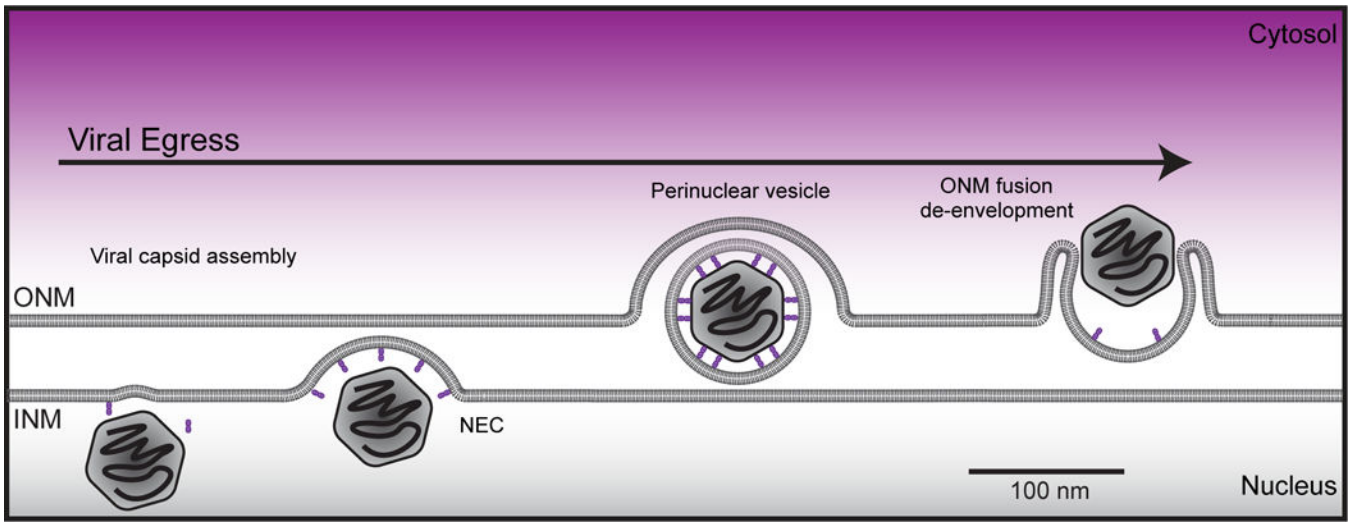

Figure 3.

Schematic of herpesvirus nuclear egress pathway. A mature viral capsid (rounded hexagon), filled with viral DNA, is recruited to the INM by the virally encoded, nuclear egress complex (NEC), which is shown in purple. The NEC deforms the INM, encapsulating the viral capsid in an intermediate perinuclear vesicle. The vesicle fuses with the ONM, in conjunction with disassembly of the NEC and release of the viral capsid into cytosol, where it further matures.

Table 1.

Genetic backgrounds with NE evagination and herniations

Gene (Genetic perturbation)	Function	Phenotype	Organism	Ref.	
NPC biogenesis/quality control					
NUP170(repression) *NUP157*(deletion)	Inner ring scaffold nucleoporins	INM-evaginations	*S. cerevisiae*	[16]	INM-evagination
POM33 (deletion)	Transmembrane nucleoporin	INM-evaginations	*S. cerevisiae*	[17]	
RTN1/YOP1 (double deletion)	Reticulon like protein (RTN1), DP1 like protein (YOP1)	INM-evaginations	*S. cerevisiae*	[19]	
STH1 (ts allele)	RSC-Chromatin Remodeling Complex	INM-evaginations, expanded PNS/NE	*S. cerevisiae*	[20]	
KAP95 (ts point mutation)	Karyopherin/Importin	INM-evaginations, ONM invagination, NE membrane rings with stacked NPCs	*S. cerevisiae*	[21]	
NTF2 (ts allele)	Nuclear transport, RanGDP binding protein	INM-evaginations, nup mis-localization, flattened/loosely stacked membranes	*S. cerevisiae*	[23]	
GLE2 (deletion or ts allele)	RNA export platform nucleoporin	NE herniations, intranuclear annulate lamellae, mRNA export defect	*S. cerevisiae*	[51]	**NE herniation**
NUP116 (deletion, or truncation)	Cytoplasmic/mRNA export platform, GLFG repeat nucleoporin	NE herniations, RNA export defect, intranuclear annulate lamellae. (C-terminal deletion results INM evaginations only)	*S. cerevisiae*	[52–54]	
NUP145N (deletion)	GLFG repeat nucleoporin	NE herniations, “grape-like” clustering of NPCs	*S. cerevisiae*	[46,55]	
NUP145N/NUP100 (double deletion)	GLFG repeat nucleoporins	NE herniations, “grape-like” clustering	*S. cerevisiae*	[56]	
NUP85 (deletion)	Y-complex/outer ring nucleoporin	clustering of NPCs, herniations, RNA export defect	*S. cerevisiae*	[38]	
NUP120 (deletion)	Y-complex/outer ring nucleoporin	NE herniations, clustering of NPCs, RNA export defect	*S. cerevisiae*	[42,43]	
NUP145C (truncation, ts allele)	Y-complex/outer ring nucleoporin	NE herniations, clustering of NPCs, RNA export defect	*S. cerevisiae*	[44]	
SEC13 (ts alleles)	Y-complex/outer ring nucleoporin, COPII coat protein	NE herniations, “grape-like” clustering of NPCs, disruption of ER network	*S. cerevisiae*	[47,48]	
NUP188 (ts allele or combination with *NUP116* GLFG deletion)	Inner ring scaffold nucleoporin	NE herniations	*S. cerevisiae*	[39–41,49]	
NUP154 (allele)	Inner ring scaffold nucleoporin	NE herniations, mis-localization of nucleoporins	*Drosophila*	[50]	
NUP57 (ts allele)	FG repeat containing	NE herniations	*S. cerevisiae*	[37]	

Gene (Genetic perturbation)	Function	Phenotype	Organism	Ref.	
	central channel nucleoporin				
MTR10/KAP111 (ts allele)	Karyopherin/Importin	NE herniations, NPC clustering. RNA export defect, expansion of PNS	*S. cerevisiae*	[22]	
ACC1 (ts allele)	Acetyl-coA carboxylase	NE herniations, expansion of PNS, RNA export defect	*S. cerevisiae*	[22,57]	
APQ12 (deletion)	Transmembrane NE protein, NE lipid composition regulator	NE herniations at 23 °C and 37 °C. Hypersensitivity to membrane fluidizers. Mis-localization of cytoplasmic filaments/RNA export platform and outer ring components at 23 °C, RNA export defect	*S. cerevisiae*	[59,60]	
BRR6 (ts allele)	Transmembrane NE protein, ill-defined function, possible NE lipid composition regulator	NE herniations at 18 °C, RNA export defect	*S. cerevisiae*	[60,74]	
BRR6, BRL1 (tandem depletion)	Transmembrane NE proteins, mostly unknown function, possible NE lipid composition regulator	NE herniations, NPC clustering	*S. cerevisiae*	[73]	
MGA2 (deletion) *SPT23* (ts allele)	Regulator of *OLE1* transcription	NE herniations, expansion of PNS, intralumenal vesicles	*S. cerevisiae*	[58]	
NPL4 (ts alleles)	Component of Ufd-Cdc48 complex, ERAD, and NE reformation in mammalian cells	NE herniations filled with electron dense material (poly-A RNA), RNA export defect	*S. cerevisiae*	[116]	
POM152/ *VPS4* (double deletion)	(*POM152*) Transmembrane nucleoporin, (*VPS4*) AAA-ATPase for ESCRT based membrane fission	NE herniations, NPC clustering	*S. cerevisiae*	[14]	
TOR1A/B/3A/2A (deletion)	Ill-defined function	NE herniations containing K48 ubiquitin labling	HeLa cells	[63]	
Torsin (knockdown)	Ill-defined function	NE herniations, abnomal DFz2C foci	*Drosophila*	[70]	
ooc-5 (knockdown)	TorA homolog, ill-defined function	NE herniations, mislocalization of nups and clustering of NPCs	*C. elegans*	[69]	
TOR1A (conditional deletion)	Ill-defined function	NE herniations, abnormal LaminA/C and Sun1 localization	*M. musculus*	[65,67,71]	
TOR1A ΔE	Ill-defined function, single amino acid deletion at aa302/303 Tor1A found in dystonia patients	NE herniations	*M. musculus*	[64]	
TOR1A EQ (overexpression)	Ill-defined function, construct with point mutation in Walker B domain at aaE171Q,	NE herniations, regions of abnormally narrow PNS	Chinese hamster ovary cells	[117]	

Gene (Genetic perturbation)	Function	Phenotype	Organism	Ref.	
	abolishing ATPase activity				
LAP1/LULL1 (knockdown)	Transmembrane Torsin co-factors, ill-defined function	NE herniations	HeLa cells	[63]	

ts = temperature sensitive