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The roles of the nuclear pore complex in cellular dysfunction, aging and disease

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Abstract

The study of the Nuclear Pore Complex (NPC), the proteins that compose it (nucleoporins), and the nucleocytoplasmic transport that it controls has revealed an unexpected layer to pathogenic disease onset and progression. Recent advances in the study of the regulation of NPC composition and function suggest that the precise control of this structure is necessary to prevent diseases from arising or progressing. Here we discuss the role of nucleoporins in a diverse set of diseases, many of which directly or indirectly increase in occurrence and severity as we age, and often shorten the human lifespan. NPC biology has been shown to play a direct role in these diseases and therefore in the process of healthy aging.

Keywords

Nuclear pore complex; nucleoporin; nucleocytoplasmic transport; aging; neurological; cancer

1. Introduction – The dynamic nuclear pore complex

Nuclear Pore Complexes (NPCs) are large multi-protein complexes that form aqueous channels bridging the cytoplasm and nucleus of all eukaryotic cells. NPCs were first visually observed by electron microscopy in 1949 in *Xenopus laevis* oocytes [1,2] and, although it is assumed that the evolution of the nucleus progressed through a protonucleus stage that was freely permeable with the cytoplasm, all extant eukaryotes possess a nucleus with NPCs [3].

After the initial discovery of the complex many experiments were done to determine the physical structure of the NPC, which was found to be a ~110 MDa structure (~60 MDa in yeast), with a central channel that allows the free diffusion of molecules less than ~90–110 Angstrom and the active transport of molecules up to ~390 Angstrom [4]. The NPC is organized into 3 basic subunits: the cytoplasmic filaments and ring, the membrane-embedded scaffold and central channel, and the nuclear ring and basket. Each of these

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components is composed of multiples of 8 copies of ~30 proteins called nucleoporins, which are arranged into a highly organized structure with 8-fold rotational symmetry. Determining the structure/number of copies of nucleoporins per NPC is still a field of active research [5].

Previously it was thought that the nucleoporin composition of all NPCs was constant and the NPC was a passive structure, which served to allow diffusion of molecules between the cytoplasm and nucleus [2,6,7]. This view was supported by the high evolutionary conservation of the NPC architecture and of the fold type, domain organization, composition, and modularity of the nucleoporins [8]. Research over the last 25 years has demonstrated that not only does the protein composition of NPCs differ between different organisms, but it also differs between cells in a single organism [9].

Tissue specific differences in NPC composition were first described with the example of Nup210. This transmembrane nucleoporin is expressed at different levels in various tissues and during different stages of development [10,11]. Depleting Nup210 in mouse cell culture models was sufficient to prevent myogenic and neuronal differentiation [12]. Since Nup210, several other nucleoporins have been shown to have differential expression between different cells and tissues, and a few other pore components have also been found to be critical for differentiation *in vitro* and *in vivo* [13–16].

In addition to the main function of NPCs as mediators of nucleocytoplasmic transport, NPCs have been shown to regulate many cellular processes in a transport-independent manner including gene expression, chromatin organization, and cell cycle regulation. The transport-dependent and transport-independent roles of NPCs were reviewed recently [17,18].

Much of the seminal work in NPCs has been carried out in yeast, which, despite having a closed mitosis (where the nuclear envelope does not break down during cell division), has been used as a model organism to demonstrate many fundamental aspects about the assembly and structure of the NPC that also hold true in metazoans. This review will focus on the role of NPCs in development, aging, and disease with an emphasis on the effect on human health. Although yeast and other single-celled eukaryotes possess characteristics that allow them to be studied to answer questions about aging and disease [19], they are evolutionarily divergent from mammals and findings in these organisms many times do not translate to humans, so we will focus our analysis on more closely related eukaryotic model organisms and studies from humans.

Most of the nucleoporin homozygous knockout mice that have been reported so far die in embryogenesis or shortly after birth. Of the few specific nucleoporin null mice that survive early development some are sterile and others have phenotypes that shorten their lifespan. Even mice with reduced levels of nuclear pore components often have serious health problems (Table 1) [13,20–37]. These studies and other examples of NPC biology will be discussed below demonstrating the importance of nucleocytoplasmic transport, nucleoporins, and NPCs in disease and healthy aging.

2. NPCs in neurological disorders and the aging brain

2.1. Triple A syndrome

The most well studied nucleoporin-related neurological disorder is called triple A syndrome. Achalasia-Addisonianism-Alacrima or Allgrove syndrome is a rare autosomal recessive disorder characterized by adrenocorticotropin resistant adrenal cortex, inability to relax esophageal sphincter, and inability to produce tears as well as other neurological symptoms [38]. The symptoms are highly variable in both severity and timing but because of the clear autosomal recessive inheritance pattern, genetic mapping of the mutation was possible. The disease was mapped to mutations in the AAAS gene, which codes for the protein Aladin [39]. At the time of the genetic mapping the subcellular location of Aladin was not known but it was subsequently found to be a component of the NPC [40]. There are many known Aladin mutations that have been linked to triple A syndrome but the ones with the greatest disease severity cause Aladin to not localize correctly to the NPC [41]. Surprisingly, Aladin knockout mice have only mild neurological defects and no other symptoms associated with triple A syndrome (Table 1) [36].

Although there is extensive information about the different mutations in the AAAS gene and there are descriptive models regarding how the nucleoporin mutations might lead to triple A syndrome, there is little evidence supporting a molecular mechanism. Aladin is directly anchored to the NPC by the transmembrane nucleoporin NDC1 [42]. Depletion of NDC1 not only affects Aladin NPC-anchoring but also impairs nuclear import [43]. Thus, an Aladin mutant that does not bind NDC1 will need to be used to discern if Aladin mislocalization results in a transport defect or if this is due to NDC1 depletion. But supporting a potential role for Aladin in nucleocytoplasmic transport, recent evidence suggests that triple A syndrome might be caused by the inability of the mutant or null allele of Aladin to transport proteins that are critical to protect cells from oxidative damage [44]. Nuclear import of a protein with known roles in oxidative stress response, Ferritin heavy chain (Fth1), is impaired in the absence of Aladin [45,46]. Subsequent research has shown that Aladin interacts directly with progesterone receptor membrane component 2 (PGRMC2), a microsomal protein known to regulate cytochrome P450 hydroxylases and oxidoreductases, which are critical for maintaining cellular oxidative state and for generating precursors for hormones like cortisol [47]. After Aladin knockdown, the cytochrome P450 enzymes are reduced and cells are more susceptible to oxidative stress [48]. These results support the hypothesis that Aladin mutations cause triple A syndrome by reducing the cells' ability to respond to oxidative stress and possibly altering hormone production.

Supporting the oxidative stress model, Aladin-depleted human adrenal tumor cells had increased levels of oxidative damage and reduced cortisol production [49]. Cortisol is normally produced by the adrenal glands in response to ACTH but one of the characteristics of triple A syndrome is insufficient cortisol production in response to ACTH [38]. This is the first human evidence demonstrating how Aladin may be causing at least one of the symptoms of triple A syndrome, but much work remains to determine how the diverse symptoms of triple A syndrome manifest from Aladin mutations. The mechanistic studies to date have demonstrated that the loss of the Aladin protein leads to toxic cellular damage, but

it sill remains to be seen if the known human mutations in the AAAS gene could cause this same damage. Additionally, how this cellular damage could cause the remaining physiological symptoms of triple A syndrome is still unclear.

2.2. Frontotemporal dementia, amyotrophic lateral sclerosis and Parkinson's disease

Frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD) are all serious neurodegenerative disorders that cause progressive loss of cognitive ability (Figure 1). In recent years a link between these disparate disorders and NPC biology has emerged. A recent example of this connection is that a motor neuron specific knockout of Nup358 (also known as RanBP2), a cytoplasmic filament nucleoporin with known roles in oxidative stress response [50], causes a mouse ALS phenotype (Table 1). Conditional ablation of Nup358 in mouse motor neurons causes the onset of the ALS symptoms of hypoactivity, hind limb paralysis, respiratory distress, and eventually death [51]. The ubiquitous Nup358 heterozygous null mice suffer from increased severity of akinetic PD when they are exposed to the neurotoxin MPTP (Table 1) [52]. The connection between PD and ALS has not been determined, but Nup358 does appear to play a role in both of these neurodegenerative phenotypes.

The first discovered genetic determinant of FTD and ALS is the GGGGCC (G_4C_2) hexanucleotide repeat expansion (HRE) found in the *C9orf72* gene. The HRE causes the transcription of RNA that form into nuclear foci [53,54]. Because the G_4C_2 HRE RNA undergoes repeat-associated non-AUG (RAN) translation, it forms insoluble high molecular weight polydipeptides [55,56]. Two groups simultaneously reported that, in Drosophila, the G_4C_2 HRE disrupts nucleocytoplasmic transport and causes the neurodegeneration typical of ALS [57,58]. Specifically, nuclear import is impaired and genetically increasing import or decreasing export rescues the neurodegeneration defect. The nucleocytoplasmic distribution of Ran in induced pluripotent stem cells (iPSCs) derived from patients with ALS is shifted towards the cytoplasm as expected in cells with reduced import. Excitingly, transport defects and neurodegeneration are rescued by pharmacotherapeutic intervention with nuclear export inhibitor KPT-276 (an analog of KPT-330, now known as Selinexor) opening up the possibility that these inhibitors might be useful for the treatment of ALS or other neurodegenerative diseases where nucleocytoplasmic transport is altered [57]. Nucleoporins were found to play a complex role in this Drosophila model of ALS. Knocking down most nucleoporins enhanced the phenotype while knocking down other nucleoporins suppressed the phenotype [58].

RAN translation of the sense and antisense G_4C_2 HRE RNAs produce 5 different polydipeptides: Poly glycine-alanine (GA), glycine-arginine (GR), glycine-proline (GP), proline-arginine (PR), and proline-alanine (PA) [59]. The formation of polyGA aggregates was prevented when a mutated form of the protein (a single proline amino acid was inserted every 5 repeats) was expressed instead of the pure polyGA variant. Toxic polyGA protein aggregates contain HR23A and HR23B (proteins critical for transferring ubiquitinated proteins to the proteasome) and nucleocytoplasmic transport proteins including the transmembrane nucleoporin Pom121 [60]. In a yeast genetic screen for polydipeptide repeat toxicity, the nucleoporin NDC1 and proteins critical to nucleocytoplasmic transport and

regulators of the Ran-GTPase cycle were found [61]. The last few years of research into the pathological mechanisms of ALS increasingly suggest an important role for nucleocytoplasmic transport and the NPC. Thorough evaluations of the role of nucleocytoplasmic transport in ALS have been conducted recently [62,63].

2.3. Huntington's Disease

Similar to the *C9orf72* HRE commonly found in ALS, a CAG repeat expansion in the *huntingtin* gene leads to the formation of polyglutamine (polyQ) protein aggregates and causes Huntington's disease (HD). HD is an autosomal dominant neurodegenerative disorder associated with neuronal cell death, motor impairment, personality changes, and dementia [64]. A mouse line with greater than 100 CAG repeats in the huntingtin gene was found to die at an advanced age after suffering from the development of a disease which possessed hallmark symptoms of HD. These mice formed neuronal intranuclear inclusions, which are also seen in patients with the disease [64,65]. Mutant forms of the huntingtin gene with greater than 20 CAG repeats cause perinuclear aggregates of the protein to form that are resistant to proteolytic degradation and cause cell death [66]. Protein aggregation in the cytoplasm but not the nucleus of cells leads to the mislocalization of proteins with low-complexity and disordered regions such as nuclear transport factors [67].

Debate exists about the subcellular location of the initial polyQ aggregates [68]. Although mutant huntingtin protein is seen to accumulate initially in the nucleus of neurons in HD mouse models [69], cell culture live imaging studies suggest that mutant huntingtin protein exists diffusely in the cytoplasm and nucleoplasm of cells and that aggregates can form on either side of the nuclear membrane. When aggregates begin to form in the cytoplasm, they eventually become perinuclear deforming the nucleus and causing the normally postmitotic cells to re-enter the cell cycle and undergo cell death. Alternatively, if aggregates formed on the inside of the nucleus, the cells would not develop cytoplasmic aggregates and continue to survive [70]. Despite the disagreement about the initial subcellular location of the aggregates, clearance of mutant huntingtin protein via the autophagy or the ubiquitin proteasome pathways and maintaining efficient nucleocytoplasmic transport is thought to be critical to preventing the disease [68].

In a mouse model of HD, after polyQ aggregates formed, nucleocytoplasmic transport was greatly impaired, nucleoporins were severely mislocalized and they were labeled less with the posttranslational modification O-linked beta N-acetylglucosamine (O-GlcNAc) [71]. Many nucleoporins are constitutively modified with the O-GlcNAc carbohydrate on serine and threonine residues [72] and these modifications are critical to prevent NPC ubiquitination and subsequent proteasomal degradation. Loss of the O-GlcNAc modification from nucleoporins leads to the disruption of the permeability barrier of the NPCs [73]. Overexpression of nucleoporins and treatment with Thiamet-G, which inhibits the O-GlcNAc removing enzyme O-GlcNAcase [74], rescues not only the transport defect but also prevents the cell death associated with the formation of the polyQ aggregates [71].

Interestingly, some of the large perinuclear polyQ aggregates are decorated with NPCs even though the nuclear envelope continues to separate the aggregates from the nucleoplasm [70]. Unfortunately, it is not yet known how or why the NPCs come to encircle the perinuclear

polyQ aggregates, but a proteomic analysis of all the proteins present in polyQ aggregates found many, if not all, nucleoporins [75]. Many questions remain about the role of NPCs in HD but there is sufficient evidence to indicate that alterations in nucleocytoplasmic transport are integral to the pathology of the disease.

2.4. Alzheimer's disease

Alzheimer's disease (AD) is a serious neurodegenerative disorder characterized by memory loss, cognitive dysfunction, and eventually early death. The prevalence of the disease is expected to quadruple in the next few decades and place an increasing burden on society [76]. The most common form of the disease has a genetic contribution of ~60–80% but no exact mechanism has been demonstrated. AD is difficult to diagnose early but can be characterized by the occurrence of extracellular amyloid beta protein aggregates, hyperphosphorylated tau (a microtubule associated protein), and intracellular neurofibrillary tangles (NFTs) composed of tau protein [76]. The role of NPCs in AD has not been established but in AD patient hippocampal neurons importin alpha1 is aberrantly localized to cytoplasmic inclusions [77], NPCs are found in aggregates, and nuclei are abnormally shaped [78].

The intracellular NFTs are analogous to the PolyQ aggregates seen in HD and the PolyGA aggregates seen in ALS because they all represent a failure in proteostasis, the cellular homeostasis of protein concentration, conformation, and location [79]. The evidence for the role the PolyQ and PolyGA aggregates play in nucleocytoplasmic transport is considerable and, while there is still little evidence that in AD NFTs might also alter transport, it seems likely that this disorder will also be found to have a critical NPC aspect.

2.5. Neurological development and brain injury

A study of the expression of nucleoporins in rats after a reduced blood flow brain injury called cerebral ischemia, found that nucleoporins Nup210, Nup107, Nup205, and Nup50 were all increased within days after the injury and the expression continued to rise for up to 4 weeks. RanGap1, an NPC binding protein with known roles in nucleocytoplasmic transport, was also found to have increased expression after injury. Expression of the nucleoporins surprisingly shifted from the classical perinuclear pattern to an intranuclear pattern [80]. The expression pattern of other nucleoporins was not examined and these experiments are still preliminary, but the possible role of nucleoporins in the resolution or pathology of brain injuries is exciting.

The first hint that nucleoporins might play a role directly in the development of the mammalian brain came from a study showing that mice a knockout of the nuclear basket nucleoporin Nup50 develop lethal neural tube defects *in utero* (Table 1) [32]. Additionally, scaffold nucleoporin Nup133 deficient mice are embryonically lethal and fail to develop terminally differentiated neurons (Table 1) [13]. Work looking at the role of NPCs in neurological development is still preliminary but there is corroborating evidence from cell culture assays. Knockdown of the transmembrane nucleoporin Nup210 prevents the differentiation of stem cells into neurons *in vitro* [12] and conversely knockdown of Nup153

in mouse embryonic stem cells induced differentiation into neurons with the associated loss of pluripotency [81].

2.6. Other neurological disorders and the aging brain

Infantile bilateral striatal necrosis (IBSN) is a neurological disorder characterized by the degradation of 2 to 3 specific areas of the brain: the caudate nucleus, the putamen, and sometimes the globus pallidus. A familial autosomal recessive form of the disease was discovered that was mapped to a Nup62 missense mutation. Surprisingly, the mutation did not cause the protein to be degraded or mislocalized [82]. How the mutated Nup62 protein leads to this disorder has yet to be determined.

Human lethal congenital contracture syndrome-1 (LCCS1), also known as fetal motor neuron disease, can be caused by a mutation in the predicted nucleoporin Gle1 [83]. A Zebrafish model showed that Gle1 is important for the survival of a subset of neuronal stem cells as well as arborization of axons [84]. In human cells the mutated form of the protein impairs Gle1 oligomerization, which is critical for the nucleoporin's role in mRNA export [85].

Nup358 mutations have been shown to cause acute necrotizing encephalopathy (ANE), which is a sporadically occurring encephalopathy that presents in children after common viral infections (Figure 1) [86,87]. It is not known if the nucleoporin mutations are related to the infection or resolution of the viral response or what possible mechanism might cause the disease to occur in patients with the mutations.

Most but not all of these neurological disorders occur more frequently and more severely with age (Figure 1). Thus far we have not directly addressed the effect of aging on the NPCs in the brain and there are not many studies that directly look at this topic but the data that does exist warrants further study. Electron microscopy studies in rats show the density of NPCs in hippocampal neurons as the brain ages drops in the dentate gyrus but stays constant in the CA1 region [88,89]. A molecular study of aging rat brains shows that scaffold nucleoporins turn over at a finite but very slow rate while peripheral nucleoporins turn over much more quickly. Consistent with previous work using *C. elegans*, this study found that the number of NPCs did not change while the relative nucleoporin composition of NPCs were altered as rats aged [90–92]. This is interesting because NPCs undergo oxidative damage and become more leaky with age [90], suggesting that the NPC turnover rate is possibly too slow and damaged NPCs accumulate with age in long lived cells such as neurons.

3. NPCs in viral infections and immunity

3.1. NPC-based viral nuclear entry

As stated above, molecules larger than ~390 Angstrom are unable to pass into the nucleus, therefore large viruses such as herpes simplex virus (HSV), human immunodeficiency virus (HIV), and adenovirus need to use 1 of 3 established methods for entry to the nucleus: 1) capsid degradation in the cytosol followed by classical nuclear import, 2) docking at the NPC followed by capsid degradation and modified nuclear import, and 3) docking at the

NPC followed by direct injection into the nucleus [93]. Even smaller viruses such as hepatitis B virus depend on nuclear entry, which is based on an active transport mechanism [94]. All of these methods involve the NPC either directly or indirectly. As we will see, viruses have evolved mechanisms to utilize the nucleocytoplasmic transport function of their hosts and their hosts have evolved mechanisms to combat these viral nuclear entry methods.

Nucleoporins that, under normal conditions, play a role in nuclear import are likely targets of viruses to establish nuclear entry. Nup214, a cytoplasmic ring nucleoporin with known roles in nucleocytoplasmic transport directly interacts with and acts as the functional import receptor of adenovirus 2 nucleocapsids [95]. The nuclear basket nucleoporin Nup153, which plays direct roles in importin alpha/beta mediated protein import [96], binds to the HIV capsid and knockdown of this nucleoporin reduces capsid entry [97]. In a proteomic analysis of HCV capsid interacting proteins, Nup98 was identified as critical for HCV entry into the nucleus and the subsequent propagation of the virus [98]. A nucleoporin found on both faces of the NPC, hCG1 [99], binds to the HIV protein Vpr and this interaction aids in the nuclear import of the viral protein [100]. These examples highlight how viruses utilize a variety of host nucleoporins, regardless of the NPC structural component, to gain entry into the nuclei of their hosts.

3.2. Antiviral immunity and evading the host immune defense

When a viral infection occurs mammalian cells produce an antiviral immune response to dampen virus production or signal for apoptosis. The most characterized example is that infected cells secrete Type 1 interferons (alpha and beta), which signal to nearby cells to activate an antiviral immune response [101]. For a virus to successfully propagate, it must evade or inhibit this antiviral immune response. Viruses are known to utilize many different methods to continue their proliferation and, considering the importance of nucleoporins in gene expression regulation [18], it is not surprising that viruses have evolved to utilize the NPC.

For example, the immune response to vesicular stomatitis virus (VSV) infection requires mRNA export, which occurs through the complex of NPC central channel nucleoporins Nup98 and Rae1. In order to block the host cell immune response, VSV produces a protein called matrix. The viral protein binds to Nup98/Rae1 and inhibits mRNA export which would effectively shut down the immune response, but immune cells such as lymphocytes produce the cytokine Type 2 interferon (IFN-gamma) which upregulates Nup98 protein to saturate the VSV block on export and allows an effective response to the intracellular pathogen [102,103]. Also targeting the role of Nup98 in antiviral signaling, polioviruses induce Nup98 degradation shortly after infection [104].

Nup98 is not the only nucleoporin targeted to alter nucleocytoplasmic transport. Human rhinovirus encodes the 2A protease family, which proteolytically cleaves Nup62, a central channel nucleoporin with known roles in nucleocytoplasmic transport [105–108]. Different strains of the rhinovirus produce variants of the 2A proteases, which cleave Nup62 in distinct ways. Nup62 cleavage changes nucleocytoplasmic transport receptors depending on how the nucleoporin is cleaved, which partially explains some of the differences in disease phenotypes and host responses to the different rhinovirus strains [109]. The nuclear basket

nucleoporin Nup153 is also degraded during picornavirus infections such as poliovirus and rhinovirus [105,106].

Viruses are also able to modulate the selectivity of the host NPC to directly favor viral proliferation. Herpes simplex virus (HSV-1) protein ICP27 directly binds Nup62 and inhibits nuclear import. At the same time ICP27 also plays a role in nuclear export of viral mRNA and protein. This allows ICP27 to simultaneously block host nuclear import receptors, which prevents an antiviral response and facilitates viral production [110]. A more in-depth review of the viral modulation of nucleocytoplasmic transport has been conducted recently [111].

It is interesting to consider if treatment with drugs that block nucleocytoplasmic transport could be used to treat a viral infection or if they could help elucidate the mechanisms used by viruses to hijack cellular transport machinery. There is some precedent for this idea. Chromosome region maintenance 1 (CRM1) nuclear export inhibitor Leptomycin B (LMB) blocks export of p53 which would be targeted for degradation in the cytoplasm by an HPV protein after HPV infection [112]. LMB also blocks mRNA export of an HIV protein critical to viral replication preventing HIV replication in monocytes [113]. Notably, Selinexor, an analog of the nuclear export inhibitor LMB, is in clinical trials for the treatment of many cancers. Because Selinexor has already proven safe enough for clinical trials, if nuclear export inhibitors are shown to be an effective treatment for viral infections, many of the barriers to approval are already reduced.

3.3. The role of nucleoporins in the immunological response

As we have seen the role of nucleoporins in virology and antiviral responses has been well studied, but the role of these proteins in immunological responses to not just viruses but also other infections is still preliminary. In a monocyte cell line the scaffold nucleoporin Nup85 (FROUNT) was found to bind CCR2 and CCR5: chemokine receptors responsible for signaling for cell motility. The binding is essential to CCR2/CCR5 signaling for pseudopodia formation and chemotaxis [114,115]. Surprisingly, in these studies Nup85 was found mainly not at the NPC but at the leading edge of the cells.

Demonstrating the first *in vivo* evidence of a nucleoporin modulating the immune response heterozygous null mice for the scaffold nucleoporin Nup96 were shown to have an impaired response to viral infections (Table 1). The mice have a specific reduction in Nup96 with normal levels of other nucleoporins and normal numbers of NPCs. Lower Nup96 protein levels specifically reduce export of mRNA for major histocompatibility complexes (MHC) I and II. Because MHCs are critical for antigen presentation to immune effector cells, the immune response to virus in these mice was dampened [30]. Like Nup96 heterozygous mice, mice with hypomorphic Sec13, a scaffold nucleoporin found in a subcomplex with Nup96 [116], have reduced MHC I and II expression and lower levels of cytokine production in stimulated T cells (Table 1) [20]. Both of these mouse models demonstrate the importance of nucleoporins in antigen presenting cells.

A direct role of nucleoporins in effector cells of the immune system has yet to be shown *in vivo* but, in a mouse T cell line, binding of the immune adaptor SLP-76 to NPC cytoplasmic

filament-associated protein RanGap1 is required for nuclear entry of SLP-76 and other proteins critical for an effective immune response [70].

4. NPCs in the development and progression of cancers

The roles of nucleoporins in a broad spectrum of cancers have been reviewed extensively [117–120]. We will briefly examine the literature in the context of the overall effect on healthy aging and highlight some newer findings. The role of nucleoporins in cancer can be put into 2 broad categories: fusion proteins and altered gene expression.

4.1. Oncogenic nucleoporin fusion proteins

Over the years, several nuclear pore complex components have been found as part of chromosomal translocations that generate aberrant fusion proteins in cancers. Tpr, Nup98, Nup358, and Nup214 are termed 'promiscuous' because they fuse to different partners to produce a variety of oncogenic fusion proteins [117].

Tpr (translocated promoter region) was the first nucleoporin described as a fusion protein [121]. Although unknown at that time, Tpr is a nuclear basket nucleoporin, which forms filaments that extend inside the nucleus. In Drosophila, the Tpr homolog Megator and another nuclear basket nucleoporin, Nup153, bind to ~25% of the genome [122]. In different cancers Tpr is found fused to 4 different tyrosine kinase receptors Met, NTrk1, FGFR1, and ALK. All of these fusions have been shown to create or are predicted to create constitutive activators of growth pathways including the Ras/MAPK and PI3K pathways [118].

The cytoplasmic filament nucleoporin Nup214 is another nucleoporin found as part of oncogenic fusion proteins. In T cell acute lymphocytic leukemia (T-ALL) and acute myeloid leukemia (AML) Nup214 is commonly fused to Dek and Set, which are modifiers of chromatin structure [123]. Nup214 also forms an active tyrosine kinase fusion protein with Abl and functions as an adaptor protein with SQSTM1 [124,125]. Although they are less well characterized than the Nup98 fusions described later, some mechanisms have been demonstrated for Nup214 fusion proteins. Recently, the Set and Dek fusions to Nup214 have been shown to alter gene expression regulation by inhibiting nuclear export of mRNA and transcription factors by tethering the export factors Crm1 and Nxf1 to nucleoplasmic aggregates [126]. In various cancers another cytoplasmic filament nucleoporin, Nup358, is fused to Alk, Abl, and Fgfr. The mechanism of oncogenesis in these fusions is still largely unexplored [117].

The central channel nucleoporin Nup98 has been shown to play a key role in cancer as a fusion protein with many binding partners that promote transformation in leukemias [118]. The Nup98/HoxA9 fusion was simultaneously first reported by two groups [127,128] and has subsequently been shown to be sufficient to cause leukemic transformation in human cells and *in vivo* in mice [129]. HoxA9 is one of a family of transcription factors, called homeodomain proteins, which are known to control development and differentiation, and are commonly mutated in cancers. Nup98 has also been found fused to other homeodomain proteins as well as non-homeodomain proteins in leukemias having ~32 known fusion partners [117].

Much research has been done studying the different Nup98 fusion proteins and many mechanisms of oncogenesis have been proposed. The homeodomain fusions exogenously upregulate HoxA cluster genes, inhibit differentiation, and increase self-renewal [130]. Recently, Nup98 fusion proteins were found to alter nuclear envelope morphology, which further expands the possible mechanisms [131]. Additionally, Nup98 fusions to TopII beta and SETBP1 were shown to displace wild-type Nup98 and subsequently reduce Crm1-dependent nucleocytoplasmic export [132]. More recently, a variety of Nup98 fusion proteins were shown to interact with mixed lineage leukemia 1 (Mll1) and these interactions are necessary for binding to Hox gene promoter regions [133]. The therapeutic implications are that Mll1 will be a good drug target in Nup98 fusion-induced leukemia.

The Nup98-HoxA9 fusion protein is found to reside in the nucleoplasm of cells [134] and many of the fusion partners have known roles in the nucleus such as histone acetyltransferases and deacetylases. Recent evidence shows that expression of Nup98-HoxA9 fusion protein in mouse embryonic stem cells induces Hox cluster genes by binding to Crm1, which is bound at specific sites. The Crm1 inhibitor LMB disassembles the fusion protein clusters and reduces the expression of the Hox genes [135]. These data are particularly interesting as this could be a secondary mechanism of action for nuclear export inhibitors, which would increase the efficacy of the drug in Nup98-HoxA9 fusion positive cancers.

4.2. Changes in nucleoporin expression and nucleocytoplasmic transport

Expression of the cytoplasmic ring nucleoporin Nup88 is elevated in cancer cell lines and many tumors [136]. Nup88 is known to interact with mitotic spindles and its overexpression causes an increase in aneuploidy [137]. The overexpressed nucleoporin is found in aggregates in the cytoplasm and higher expression correlates with cancer progression and poor prognosis [138,139]. A recent study has mapped the interactome of Nup88 and demonstrated that the nucleoporin blocks Misp spindle localization that is critical for normal spindle formation and chromosome separation [140].

An analysis of proteome alterations during prostate cancer progression revealed that Nup62 is upregulated in metastatic and clinically localized prostate cancer when compared to benign prostate [141]. Nup62 was shown to directly regulate calcium signaling through calmodulin-dependent kinase kinase 2 (CaMKK2) in castrate resistant prostate cancer cells. Nup62 and CaMKK2 expression are increased in advanced prostate cancer and knockdown of Nup62, and not other nucleoporins (Nup98 or Nup88), reduced growth more strongly in an advanced prostate cancer cell line when compared to a non-malignant prostate cell line [142].

NDC1 is highly overexpressed in NSCLC and higher expression levels correlate with increased progression and poorer survival. Knockdown of NDC1 in NSCLC cell lines reduced cell proliferation and caused cell cycle alterations. *In vivo* knockdown of NDC1 in xenograft cancer models was able to reduce tumor growth [143].

Although the mechanisms of pathogenesis are not well characterized, most other nucleoporins and transport proteins have also been found dysregulated in various cancers

including Nup210, Nup133, Nup107, Sec13, Nup188, Nup93, Nup153, Tpr, Nup358, Nup214, Nup98, hCG1, RanGap1, and Rae1 [117,144].

Interestingly, in a whole genome RNAi screen against colon cancers with expression profiles similar to *Braf(V600E)* mutants, Nup358 was the gene found to have the greatest specific lethality when knocked down. The Braf-like mutant colon cancer cells depended on Nup358 for efficient microtubule dynamics at kinetochores and the cells were more sensitive to the microtubule polymerizing poison vinorelbine. Treatment with vinorelbine was sufficient to block Braf-like mutant colon cancer xenograft tumor growth [145]. The critical role for Nup358 in mitotic spindle assembly was previously described in HeLa cells [146] but this study highlights how nucleoporins are capable of playing roles in cancer pathogenesis while not directly associated with the NPC and without being fused to other proteins. The example of Nup62 seen above and this case of Nup358 demonstrate how targeting nucleoporins, even ubiquitously expressed ones with broad cellular roles, can have differential lethality in cancer cells.

Thus far we have discussed the direct role of NPC components in cancer, but new research suggests that nucleocytoplasmic transport through the NPC may play a role in some forms of cancer. Not surprisingly, potent inhibitors of nuclear export like Leptomycin B prevent growth of cells including cancer cells. Recent work has shown that the selective inhibitor of nuclear export, Selinexor, is capable of specifically inhibiting the growth of human leukemia cells with little toxicity to the hematopoietic cells in a mouse model [147]. This form of treatment has proved effective and safe enough to enter into multiple late stage clinical trials [148]. Additionally, it was recently published that Selinexor is specifically lethal to Kras mutant non-small cell lung cancers when compared to Kras wild type cancer cells. In these cells nuclear export was necessary to prevent the cell growth factor Nfkb inactivation by Ikba accumulation in the nucleus [149].

4.3. Nucleoporin-based mouse cancer models

As we have seen, many nucleoporins play a significant role in different cancers. With a variety of nucleoporin haploinsufficient, knockout, and overexpression mice available, it is interesting to examine if these mice are prone to cancer. In most cases, nucleoporin knockout mice are embryonic lethal and tumorigenesis has not been reported in many of the non-lethal knockout mice but overexpression and heterozygous null mice have been studied (Table 1).

In mice Nup88 overexpression was shown to cause spontaneous intestinal tumors and although global nucleocytoplasmic transport was unaffected, aneuploidy and chromosome instability were induced. The mechanism demonstrated was that high levels of Nup88 sequester Nup98-Rae1 away from APC/C^{CDH1} where they normally function to ensure correct centrosome segregation [31]. This is further proof that the role of Nup88 in cancer is mediated by its transport-independent mitotic functions.

Nup98 and Rae1 double heterozygous mice and Rae1 heterozygous mice have increased aneuploidy. The mice have a normal rate of spontaneous tumorigenesis but have a higher incidence of tumors when treated with the carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) [28].

Mice with Nup358 haploinsufficiency or hypomorphism develop severe aneuploidy from a failure to properly segregate chromosomes during mitosis. The aneuploidy manifests in an increased incidence of spontaneous tumors and DMBA-induced tumors [22]. Interestingly, in humans Nup358 levels are reduced in non-small cell lung carcinoma when compared to healthy controls [150], although a prospective study would better explain if low Nup358 levels increase the risk of this type of cancer.

5. NPCs in other disorders

5.1. Primary biliary cholangitis (PBC) and other autoimmune disorders

PBC is an autoimmune T lymphocyte mediated chronic non-suppurative destructive cholangitis (CNSDC) disease. Nup210 and Nup62 autoantibodies were found to be associated with more severe primary biliary cirrhosis and poorer prognosis [151]. Nup210 and Nup62 autoantibodies, along with automitochondrial antibodies, are so infrequent outside of the disease context that they are considered to be a biomarker for PBC [152]. Additionally, Tpr and some nuclear envelope autoantibodies have been found in PBC as well as other autoimmune disorders such as arthritis, systemic lupus erythematous (SLE) and autoimmune liver disease (ALD) [153,154].

Interestingly, Nup210 is not expressed in normal liver biliary epithelial cells, lowly expressed in hepatitis diseased liver cells, and highly expressed in PBC liver cells [155] suggesting that the abnormal expression of Nup210 in these cells may be a consequence of or play a role in the development of the diseases. Nup358 was found to play a critical role in maintaining bile acid homeostasis in biliary epithelial cells and protein levels were increased shortly after exposure to a primary biliary acid [156].

The role of nuclear envelope proteins including the nucleoporins Nup210, Nup62, and Tpr in autoimmune disorders has yet to be determined. It has been suggested that the autoantibodies seen in PBC are a consequence of molecular mimicry of bacterial antigens, which are similar to the mammalian antigens. The best evidence for this is that in a mouse model of CNSDC, mice inoculated with *Streptococcus intermedius* develop Nup210 autoantibodies [157] but, it would be informative to determine if the autoantibodies are a result of the molecular mimicry or the host antigens. Another group created a mouse model of autoimmunity in the bile ducts by inoculating mice with *Novosphingobium aromaticivorans*, and although they did not test for Nup210 autoantibodies they did demonstrate that transferring the NK T lymphocytes from mice where the disease had already been observed, was sufficient to establish the disease in recipient mice [158]. This suggests that a bacterial infection may be required to trigger the disease but PBC is mediated by the host immune system after disease onset.

5.2. Steroid-resistant nephrotic syndrome (SRNS)

Dysfunction of the glomerular podocytes in the kidney causes SRNS, which often leads to chronic kidney disease. Recently homozygous and compound heterozygous mutations in Nup93, Nup205, and Xpo5 were identified as monogenic causes of SRNS. Nup205 or Nup93 mutations disrupted NPC assembly and their knockdown reduced the presence of the

other nucleoporins at the NPC [159]. Nup107 homozygous mutations have been found that cause early childhood onset SRNS [160]. All of the nucleoporins that have been shown to be involved in SNRS are known to be members of the critical NPC scaffold. Much research remains to be done but it is possible that these mutations disrupt the formation or transport function of the NPC.

5.3. Cardiovascular

There is building evidence that nucleoporins play a role in the cardiovascular system. An analysis of copy number variants in humans with heterotaxy, a rare but serious birth defect that affects heart development, found a duplication event in the *Nup188* gene. Morpholino knockdown of the gene in *Xenopus* caused a defect in left-right patterning [161].

Patients who have had heart failure (ischemic and dilated hearts) have increased levels of specific nucleoporins. Specifically the transmembrane nucleoporin NDC1, the scaffold nucleoporin Nup160, and the nuclear basket nucleoporin Nup153 are increased in hearts of patients with ischemic and dilated cardiomyopathy, while Nup93 was increased only in dilated heart patients. NDC1 was also shown to be mislocalized in cardiomyocytes from both ischemic and dilated hearts [162]. Supporting these data, a point mutation in the scaffold nucleoporin Nup155 was sufficient to delocalize the nucleoporin from the NPC, which led to early sudden death due to atrial fibrillation. Additionally, Nup155 hypomorphic mice have atrial fibrillation and die of early sudden cardiac death (Table 1) [25].

The scaffold nucleoporin Nup35 has been shown to regulate intracellular cardiomyocyte pH by controlling the mRNA export of the Na^+–H^+ exchanger- 1 (NHE1) transcript [163]. NHE1 protein is responsible for maintaining intracellular pH [164]. In response to an acid challenge cardiomyocytes deficient in Nup35 failed to maintain intracellular pH homeostasis and overexpression of Nup35 blocked hypoxia-induced intracellular acidification. Both Nup35 and NHE1 are downregulated in ischemic cardiomyocytes [163].

After cardiomyocyte hypertrophic stimulus nuclear import is downregulated to increase nuclear export by changing the conformation of the cytoplasmic face of the NPC [165]. During cardiomyocyte differentiation there is a conformational change in the NPC that results in increased NPC density, larger pore size, greater likelihood of cargo occupancy, and Mef2c translocation from the cytoplasm to the nucleus [166,167]. Cardiomyocytes derived from a knockout mouse for the calcium sequestering protein, calreticulin (which is necessary for proper cardiac development) had altered NPC composition. NPCs from the knockout mouse were found to have smaller pores and Nup62, Nup214, and Nup153 were reduced even though Nup98 levels were unaffected and the density of NPCs remained the same [168]. Supporting evidence in plants for the change in conformation state of the NPC shows that the selectivity of pores can be altered in response to cellular stresses [169]. Although these studies are preliminary they suggest a new paradigm for examining the role of NPCs in development and diseases: not just composition of NPCs but conformational states can alter the fate and function of cells.

5.4. Beta Thalassemia

The insights gained from the study of Nup98 fusion proteins have led to an unexpected possible treatment for the autosomal recessive hematological malignancy Beta Thalassemia, which causes anemia from reduced hemoglobin synthesis. A Nup98-HoxA10HD fusion protein was engineered and when transfected in hematopoietic stem cells, was able to increase the proliferative ability and maintain the undifferentiated state of the stem cells *in vitro* [170]. The Nup98 fusion protein was able to increase the number of human hematopoietic stem cells 4 months after initial transfer into immunodeficient mouse hosts [171]. This strategy has been shown to be effective in the treatment of a murine model of Beta Thalassemia [172].

5.5. Aging

Aging plays a role in almost all of the diseases discussed above but the normal aging process is also involved in NPC biology. It was identified that in postmitotic tissues NPC assembly does not occur or takes place at a very low rate. In postmitotic *C. elegans* cells, expression of the scaffold nucleoporins, which are essential for NPC assembly, is unnecessary after development as NPC scaffolds do not significantly turn over for the remainder of their lives (~40–50 days). This low, or lack of turnover, of NPCs in postmitotic tissues has also been described in mammals [173]. Pulse chase experiments in cells and rats showed that scaffold NPC components turn over very slowly or not at all in postmitotic cells while non-scaffold nucleoporins are short lived [90,91]. Subsequent experiments have shown that scaffold nucleoporins do turn over but very slowly [92]. Due to their extremely long life, in aging neurons NPCs accumulate damage to the point where they can no longer perform their functions [90]. This results in the loss of nuclear compartmentalization and the abnormal distribution of nuclear and cytoplasmic proteins in old neurons, which can have devastating effects for cellular homeostasis. Similarly, recent evidence indicates that as rats age their myocytes also have compromised nuclear compartmentalization and lower levels of the structural nucleoporin Nup93 which is critical for nuclear permeability [174,175].

Nucleocytoplasmic transport is also perturbed in aging by alterations in the levels of non-nucleoporin transport proteins. In a study comparing transcriptional profiles of iPSC-derived neurons and directly reprogrammed induced neurons (iNs) from old and young humans, the nuclear import receptor RanBP17 was identified as a cause of the age-associated loss in nuclear compartmentalization. The protein is reduced in aged neurons and is necessary for maintaining nuclear compartmentalization [176].

The accumulation of protein aggregates, which have pathogenic effects in diseases like AD, have also been shown to be an inherent part of the normal aging process in *C. elegans* [177]. As discussed above, nucleoporins play a direct role in the prevention of protein aggregates and some of their negative consequences. Demonstrating that protein aggregation is inherently part of the aging in mammals would significantly expand the possible roles of nucleoporins in the aging and aging-related diseases.

The role of nucleoporins in the aging of higher eukaryotes has yet to be directly determined because many of the nucleoporin knockout mice are unable to complete embryogenesis

(Table 1) but aging and age-related diseases could be studied with the use of genetic mouse tools. Overexpression, hypomorphic, inducible knockout and inducible shRNA expression mouse lines would allow the induction, reduction or depletion of specific components of the NPC, at different times of development/disease progression, and in specific cells of the mouse. This would greatly enhance our ability to study the functions of nucleoporins in specific tissues and how those functions play a role in aging and aging-related diseases.

6. Conclusions

Many new advances in the study of nucleocytoplasmic transport, the NPC, and nucleoporins suggest that the ability of organisms to regulate these processes and structures must be tightly controlled to prevent diseases from arising or progressing. Many of the diseases discussed here are directly associated with aging such as AD and HD but most of the remaining diseases such as cancer and cardiovascular disease become worse indirectly with age. Regardless, the aging of humans increases the occurrence and severity of diseases that nucleoporins have been shown to play a direct role in (Figure 1). These diseases, and therefore nucleoporins, play at least an indirect role on human lifespan.

The original identification of a gene duplication of the Pom121 nucleoporin creating a protein called Pom121C opened up new possibilities for nucleoporins. Knocking down either Pom121 protein caused NPC clustering in HeLa cells [178]. More recently it was shown that the Pom121C gene codes for a soluble form of the protein that utilizes the Pom121 NPC interacting domains to bring a subset of nucleoporins into Nup98 nucleoplasmic clusters. Although the role of this particular gene duplication event is not known, it was found that it arose multiple times in evolutionary history suggesting that there is a convergent advantage [179]. As seen above, this process parallels the one used by cancer cells to tether or bring oncogenic transcription factors into the nucleus through nucleoporin fusion proteins. Utilizing nucleoporins to direct subsets of proteins (including other nucleoporins) to specific sites in the genome could expand the mechanisms by which these proteins are capable of altering cell function and fate as well as diseases and aging.

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Abbreviations

NPC	Nuclear Pore Complex
triple A syndrome	Achalasia-Addisonianism-Alacrima or Allgrove syndrome
FTD	Frontotemporal dementia
ALS	amyotrophic lateral sclerosis

PD	Parkinson's disease
HRE	hexanucleotide repeat expansion
RAN	repeat-associated non-AUG
GA	translation, Poly glycine-alanine
GR	glycine-arginine
GP	glycine-proline
PR	proline-arginine
PA	proline-alanine
polyQ	polyglutamine
O-GlcNAc	O-linked beta N-acetylglucosamine
NFTs	neurofibrillary tangles
IBSN	Infantile bilateral striatal necrosis
LCCS1	lethal congenital contracture syndrome-1
ANE	acute necrotizing encephalopathy
VSV	vesicular stomatitis virus
HSV	herpes simplex virus
CRM1	Chromosome region maintenance 1
LMB	Leptomycin B
MLL	mixed lineage leukemia
CaMKK2	calmodulin-dependent kinase kinase 2
DMBA	7,12-dimethylbenz[a]anthracene
PBC	Primary biliary cholangitis
CNSDC	chronic non-suppurative destructive cholangitis
SLE	systemic lupus erythematous
ALD	autoimmune liver disease
SRNS	Steroid-resistant nephrotic syndrome
NHE1	Na^+–H^+ exchanger- 1
iNs	induced neurons
iPSCs	induced pluripotent stem cells

T-ALL	T cell acute lymphocytic leukemia
AML	acute myeloid leukemia

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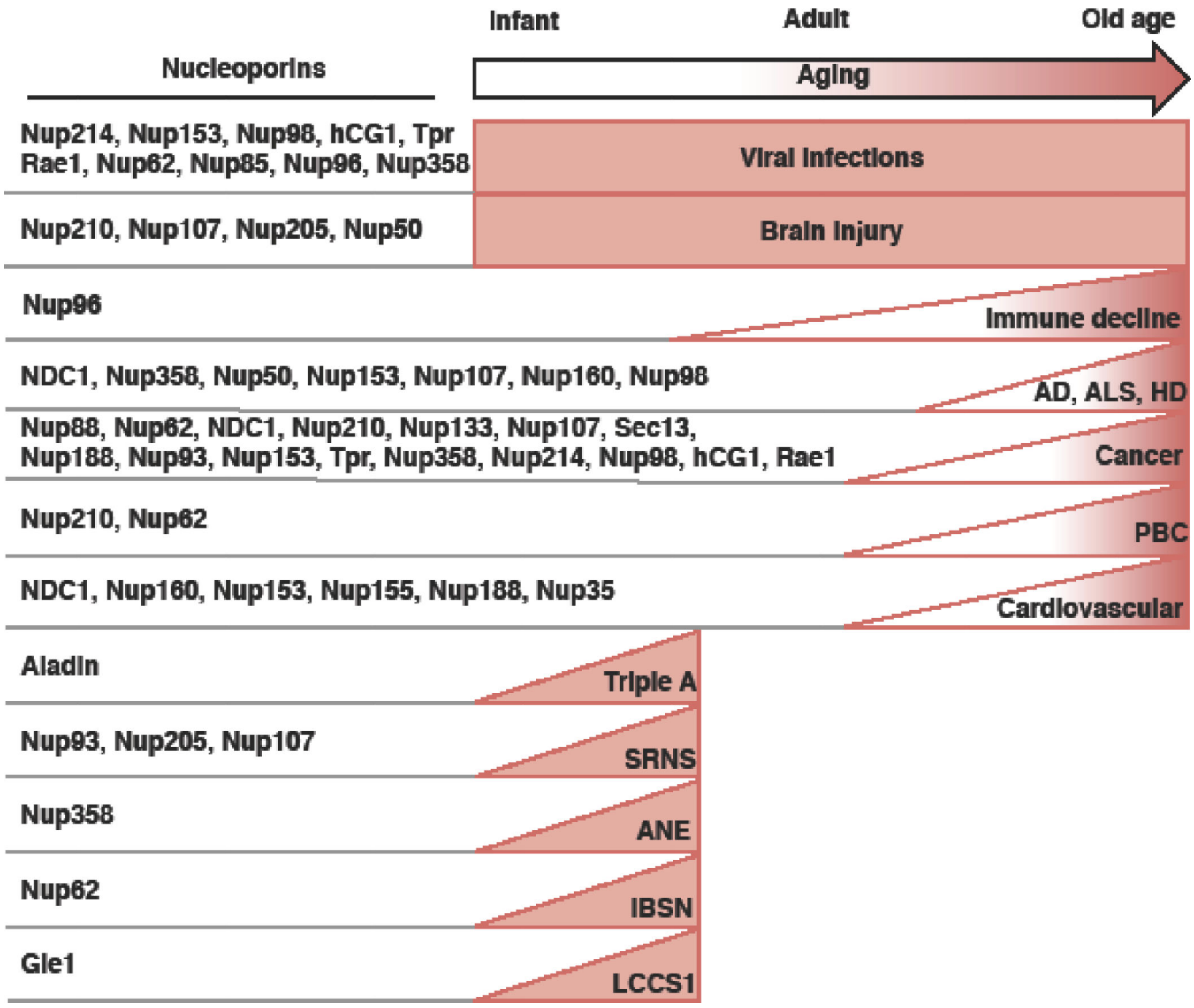

Figure 1.

Onset of nucleoporin-implicated health problems. Left: a list of the nucleoporins that are implicated in the health problems listed on the right. Right: a list of health problems with the age-based prevalence indicated by the box/triangle.

Triple A: Achalasia-Addisonianism-Alacrima or Allgrove syndrome; ALS: amyotrophic lateral sclerosis; PD: Parkinson's disease; IBSN: Infantile bilateral striatal necrosis; LCCS1: lethal congenital contracture syndrome-1; ANE: acute necrotizing encephalopathy; PBC: Primary biliary cholangitis; SRNS: steroid-resistant nephrotic syndrome

Table 1

Published phenotypes of mice possessing mutations in nucleoporins

Nucleoporin	Mutation	Phenotype	References
Aladin/AAAS	Homozygous null	Sterility	[36]
ELYS	Homozygous null	Embryonic lethality	[35]
ELYS	Intestinal epithelium null	Juvenile growth delay	[37]
NDC1	Homozygous null	Sterility and developmental defects	[34]
Nup35	F192L Mutant	Degenerative colonic smooth muscle myopathy	[33]
Nup50	Homozygous null	Embryonic lethality	[32]
Nup88	Overexpression	Increased genetic tumor model tumorigenesis	[31]
Nup88	Homozygous null	Not Viable	[31]
Nup96	Homozygous null	Embryonic lethality	[30]
Nup96	Heterozygous null	Reduced antigen presentation and immunodeficiency	[30]
Nup98	Homozygous null	Embryonic lethality	[29]
Nup98	HoxA9/HoxD13 fusion	Spontaneous leukemia	[26,27]
Nup133	Homozygous null	Embryonic lethality	[13]
Nup155	Heterozygous null	Atrial fibrillation and early sudden cardiac death	[25]
Nup155	Homozygous null	Embryonic lethality	[25]
Nup214	Homozygous null	Embryonic lethality	[24]
Nup358/RanBP2	Homozygous null	Embryonic lethality	[23]
Nup358/RanBP2	Heterozygous null	Reduced size and impaired glucose homeostasis	[23]
Nup358/RanBP2	Hypomorph	Spontaneous and carcinogen-induced tumorigenesis	[22]
Rae1	Homozygous null	Embryonic lethality	[21]
Nup98+Rae1	Double Heterozygous Null	Increased carcinogen-induced tumorigenesis	[28]
Sec13	Homozygous null	Embryonic lethality	[20]
Sec13	Hypomorph	Reduced antigen presentation	[20]