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Review

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 have 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.

Contents

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 translation; GA, 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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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 proto-nucleus 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 Å and the active transport of molecules up to ~390 Å [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 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 oxida-