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Review

Stress and aging at the nuclear gateway

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ABSTRACT

The nuclear pore complex (NPC) is a massive molecular machine embedded in the nuclear envelope and controlling traffic into and out of the cell nucleus. Here, we describe some of the outstanding research questions concerning the NPC, its assembly and functions. We also discuss recent findings that link the NPC and its immediate surroundings to the process of cellular aging. Scaffold and barrier nucleoporins are two major types of protein building blocks that make up the NPC. Surprisingly, these two groups of nucleoporins differ dramatically in their turnover rates. Recent work identifies some of the scaffold nucleoporins as the most extremely long-lived proteins in rat brain. Some of the consequences of these findings and new open questions arising from them are discussed. We also consider the evidence for a perturbed permeability barrier in nuclei from old cells and the alteration of nuclear transport pathways under stress conditions. Finally, we describe the connection between premature aging syndromes and the nuclear lamina, a filamentous protein network which underlies the nuclear envelope.

1. The nuclear envelope and nuclear pore complexes

The defining feature of eukaryotic cells is a membrane-bound nucleus, which houses the genome and separates the major steps in the gene expression pathway. The selective boundary of the nucleus is formed by the aqueous translocation channels of nuclear pore complexes (NPCs), embedded within the double membranes of the nuclear envelope (NE). The inner and outer nuclear membranes comprise two distinct phospholipid bilayers which converge into a specialized, highly curved pore-membrane domain, the site of NPC integration (Fahrenkrog et al., 2004; Gerace and Burke, 1988; Hetzer and Wente, 2009; Watson, 1959). A 40–50 nm wide perinuclear space separates the two nuclear membranes and is continuous with the lumen of the endoplasmic reticulum. Interactions between SUN and KASH domain proteins, embedded in the two membranes, bridge the perinuclear space and form additional connections with the cytoskeleton and the filamentous nuclear lamina on both sides of the NE (Burke, 2012; Goldberg et al., 1999; Sosa et al., 2012).

The NPC itself is a huge proteinaceous molecular machine composed of multiple copies of ~30 different proteins called nucleoporins (Nups). The overall architecture of the NPC is conserved from unicellular protozoans and fungi to human cells and is characterized by an eight-fold rotational symmetry around a central aqueous channel (Fahrenkrog et al., 2004; Vasu and Forbes, 2001; Wente and Rout, 2010). The structural framework (or scaffold) of the NPC is often described as a series of three concentric rings, with a central spoke-ring assembly sandwiched between cytoplasmic and nuclear rings. The massive central framework is anchored to the curved pore-membrane domain by several integral membrane nucleoporins (Beck et al., 2004; Hinshaw et al., 1992; Stoffler et al., 2003). Peripheral extensions are formed by distinctive proteinaceous filaments emanating from the cytoplasmic and nuclear rings: eight free-ended cytoplasmic filaments and eight similar filaments terminating in a distal ring, which form the "nuclear basket" (Fig. 1).

The individual protein building blocks of the NPC can be classified into three broad groups: the membrane-anchored Nups, scaffold Nups and peripheral (or barrier) Nups (Brohawn et al., 2009; Cronshaw et al., 2002; Hoelz et al., 2011). Barrier Nups constitute about one-third of NPC components in all eukaryotes and are characterized by multiple (up to 50) repeats of phenylalanine-glycine (FG) interspersed with short stretches of hydrophilic amino acids. These so-called FG repeats line the entire passage route through the NPC: from the cytoplasmic filaments, through the central channel and down to the nuclear basket (Ben-Efraim and Gerace, 2001; Ribbeck and Gorlich, 2001; Rout et al., 2000; Strawn et al., 2004). The barrier Nups are intimately linked to the holy grail of this research field: understanding the exact molecular nature of the permeability barrier and the secrets of the NPC's gating mechanism (see Section 2). Scaffold Nups are structurally conserved, modular building blocks, which are largely composed of β-propellers, α-helical domains, or a tandem combination of these protein folds (Hoelz et al., 2011; Schwartz,

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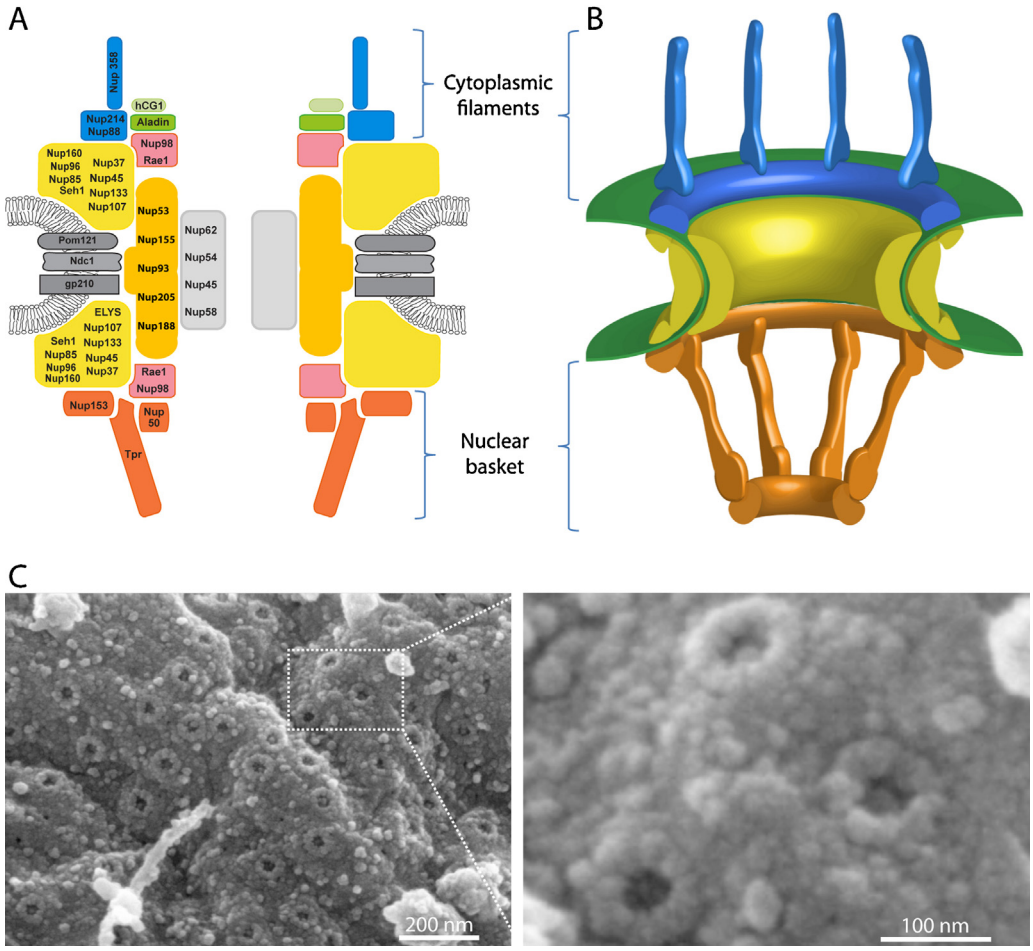

Fig. 1. The Nuclear pore complex. (A) A schematic cross-section depicting the major structural modules and subcomplexes of the NPC. Individual vertebrate nucleoporins are shown on the left side according to their approximate positions within the structure and subcomplexes are shown in different colors. The three vertebrate membrane Nups are shown in grey, integrated into the curved bilayer of the pore membrane. (B) A cross-section emphasizing three-dimensional features and the peripheral substructures of NPC architecture. The structural framework has an eight-fold rotational symmetry around the transport channel and is integrated into the membranes (green). The cytoplasmic ring moiety with attached cytoplasmic filaments (blue) and the nuclear ring with the attached nuclear basket (orange) surround the central spoke-ring assembly (yellow). (C) Direct surface Imaging of NPCs embedded in the NE of a mammalian cell nucleus. The cytoplasmic surface of the nucleus was imaged by high resolution scanning electron microscopy. Note that the sample was fixed and coated with a thin layer of chromium. For details of the preparation method, see: Shaulov and Harel (2012).

2005). Surprisingly, a common structural arrangement of these motifs has been found in several scaffold Nups and in COPII vesicle coat proteins. This has led to the "proto-coatamer" hypothesis, postulating a common evolutionary origin for key structural elements of the NPC and coated vesicles, and fueling speculation about the role of an ancestral membrane-curving module in the formation of the eukaryotic nucleus (Brohawn et al., 2008; Devos et al., 2004; Onischenko and Weis, 2011).

The general distinction between structural Nups, stabilizing the central scaffold, and barrier Nups, playing a functional role in selective gating, extends to additional properties of the NPC. As described in Sections 4 and 5, these two groups of nucleoporins differ in their residence time at the NPC and in general protein turnover rates. Intriguing new evidence links extremely long-lived proteins (ELLPs), discovered in rat brain, with scaffold Nups (Savas et al., 2012). These findings bring new aging-related questions to the nuclear transport field and renewed interest in many previous observations of stress- and aging-induced damage to the nuclear periphery (see Sections 6 and 7).

Stress response and aging are also connected to a close neighbor of the NPC: the nuclear lamina, which lines the nuclear side of the inner nuclear membrane. Nuclear lamins are the main constituents of this fibrous protein meshwork, which interacts with multiple membrane proteins, chromatin and NPCs (Burke and Stewart, 2013; Dechat et al., 2010; Goldberg et al., 1999). Numerous mutations in the genes encoding nuclear lamins and lamin associated proteins are responsible for a broad range of human diseases termed laminopathies (Worman et al., 2010). Most notably, a sporadic point mutation in the LMNA gene causes the rare premature aging disease Hutchinson–Gilford progeria (Eriksson et al., 2003). These and other connections between the nuclear boundary and cellular aging are discussed in Section 7.

2. Nuclear transport and the permeability barrier

The NPC is positioned at the very central intersection of eukaryotic cellular life. Compartmentalization, achieved by the nuclear boundary, separates many essential processes such as the transcription and processing of mRNA within the nucleus from protein translation in the cytoplasm. This creates the need for tremendous rates of bi-directional trafficking of different macromolecules across the NE (e.g., import of ribosomal proteins and splicing factors, export of tRNAs and ribosomal subunits). Most macromolecular cargoes are ferried across the NPC channel by active transport mechanisms and accumulate in their destination compartment against a chemical concentration gradient (Mattaj and Englmeier, 1998; Ribbeck and Gorlich, 2001; Weis, 2003). These tasks are carried out by a group of shuttling nuclear