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Review

Border Safety: Quality Control at the Nuclear Envelope

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The unique biochemical identity of the nuclear envelope confers its capacity to establish a barrier that protects the nuclear compartment and directly contributes to nuclear function. Recent work uncovered quality control mechanisms employing the endosomal sorting complexes required for transport (ESCRT) machinery and a new arm of endoplasmic reticulum-associated protein degradation (ERAD) to counteract the unfolding, damage, or misassembly of nuclear envelope proteins and ensure the integrity of the nuclear envelope membranes. Moreover, cells have the capacity to recognize and triage defective nuclear pore complexes to prevent their inheritance and preserve the longevity of progeny. These mechanisms serve to highlight the diverse strategies used by cells to maintain nuclear compartmentalization; we suggest they mitigate the progression and severity of diseases associated with nuclear envelope malfunction such as the laminopathies.

The Nuclear Envelope as a Nuclear Subcompartment

As the defining organelle of eukaryotes, the nucleus serves as an excellent model to identify mechanistic paradigms that generate and maintain organelle identity and function throughout the lifetime of a cell. Two concentric membranes delimit the nucleus, the 'inner' and 'outer' nuclear membrane (INM and ONM), which together comprise the nuclear envelope (NE). The NE is contiguous with the endoplasmic reticulum (ER) but is enriched in a subset of proteins (and likely lipids) that biochemically and functionally distinguish it from ER. This specialization is contributed predominantly by integral membrane proteins that localize to the INM (see Figure I in Box 1), and by nuclear pore complexes (NPCs), which mediate the bidirectional exchange of molecules across the NE (Box 2). The nuclear lamina, which is an interwoven network of the intermediate-filament like lamin proteins, that underlies the INM is also generally considered to be part of the NE, although it is not universal to all eukaryotes (Box 1). Over the past few decades, major efforts by the field have illuminated mechanisms that lead to the formation and function of the NE. These include studies aimed at elucidating how the NE is broken down and reformed during mitosis [1,2], how NPCs are assembled [3] and mediate nuclear transport [4], and how integral INM proteins are targeted to [5], and function, at the INM [6]. It is becoming clear, however, that there is a disruption in NE organization and function as cells age and in human diseases caused by NE malfunction [6,7]. These observations suggest that the capacity of a cell to maintain NE function in the context of genetic or physical perturbation will be crucial for its ultimate viability and lifespan. With this in mind, recent work is revealing quality control (QC) mechanisms that safeguard the integrity and function of the NE, while also protecting cell viability in the face of NE malfunction.

The Compartmentalization of QC

The best understood QC mechanisms are those that contribute to protein homeostasis (proteostasis) by stimulating the refolding or degradation of misfolded or damaged proteins [8,9]. The

Trends

Protein QC is compartmentalized in eukaryotes: a dedicated arm of ERAD functions at the INM to protect its unique proteome, and perhaps its lipidome as well.

The ESCRT machinery ensures the integrity of the NE membranes by sealing them at the end of mitosis.

ESCRTs help ensure the proper assembly and function of NPCs during interphase.

NPC malfunction is linked to aging: in analogy to spatial QC mechanisms, budding yeast sequester malfunctioning NPCs into a cluster that helps prevent their inheritance to daughter cells.

The loss of nuclear compartmentalization and the intermixing of cytosolic and nuclear contents is a feature of the cellular pathology of many human diseases, which might be mitigated by NE-specific QC mechanisms.

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Box 1. The Inner Nuclear Membrane Proteome

The INM is enriched with a subset of integral membrane proteins that are synthesized and inserted into the ER. The mechanism of membrane protein targeting to the INM remains a topic of active investigation and this work has been recently reviewed [5]. While there appears to be differences in the requirements for energy and/or nuclear transport receptors for the targeting of individual INM proteins, there is nonetheless consensus that membrane proteins move along the continuous bilayer from the ER/ONM, through the nuclear pore membrane, to the INM where they interact with nuclear factors including the genome and the nuclear lamina [6]. The continuity of the NE–ER system and the inability to distinguish between the INM and ONM by conventional fluorescence microscopy has made defining the INM proteome a persistent challenge in the field. Proteomic studies support that there are dozens of NE integral (NETs) proteins in mammalian cells [51], some of which are differentially expressed in tissues [91] but not all are known to localize exclusively to the INM; yeast have far fewer with only a handful clearly identified (Figure I). In metazoans, many integral INM proteins bind to the nuclear lamina, which is a network of intermediate filament-like proteins made up of A- and B-type lamins (Figure I). The lamins provide mechanical stability to the nucleus, contribute to the NE tethering of chromatin that is largely transcriptionally silent, and influence signaling pathways [92]. While not present in all eukaryotes, the prevalence of human diseases associated with mutations in the lamin-encoding genes (*LMNA* and *LMNB*) have made understanding lamin function a priority [6,83].

The most conserved integral INM proteins from yeast to humans are members of the LAP2–emerin–MAN1 (LEM) [93] and the Sad1–Unc84 (SUN) families [94], categorized by the presence of the 'LEM' and 'SUN' domains (Figure I). The LEM domain is a 40–50 amino acid helix extension helix motif that interacts with (at least in metazoans) the chromatin-binding factor barrier-to-autointegration factor (BAF), but likely also with DNA and other proteins [93,95]. The SUN domain proteins are found within the perinuclear space/NE lumen and exist as trimers that bind three KASH domain proteins at the ONM (Figure I). The binding of the KASH proteins with cytoplasmic cytoskeletal elements mechanically couples the cytoskeleton with chromatin, raising the possibility of the direct mechanical modulation of genomic processes [96].

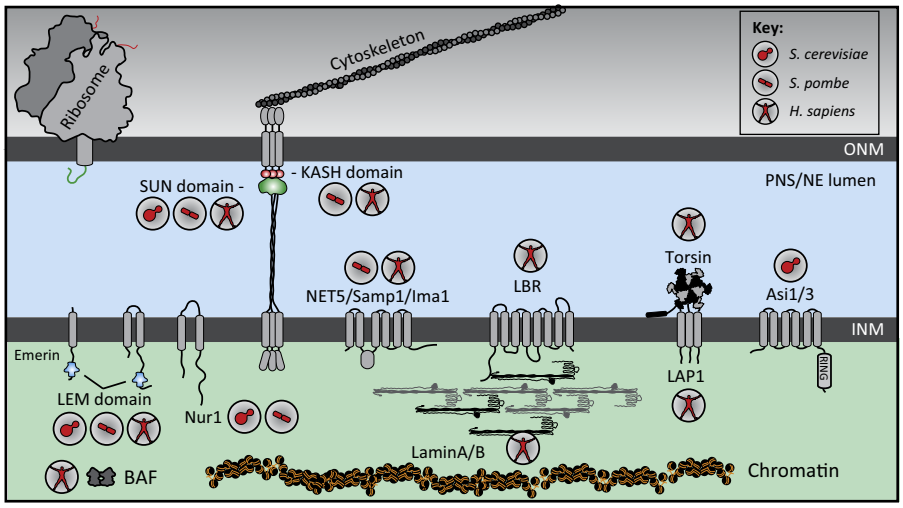

Figure I. Common Integral Membrane Proteins of the Nuclear Envelope (NE) and their Evolutionary Conservation. The most conserved membrane proteins at the INM contain the LEM (blue) and SUN (green) domains. The KASH domain (red) is also well conserved, although no clear KASH domain ortholog has been identified in *Saccharomyces cerevisiae*. Abbreviations: INM, inner nuclear membrane; ONM, outer nuclear membrane; PNS, perinuclear space; LEM, LAP2–emerin–MAN1; SUN, Sad1–Unc84.

gradual loss of these mechanisms is thought to contribute to the age-related decline of cellular function, and to the accumulation of toxic misfolded protein aggregates characteristic of the pathology of neurodegenerative disorders such as Alzheimer's or Huntington's disease [10]. Interestingly, toxic protein species often accumulate in cellular organelles such as the nucleus [11], which suggests that QC mechanisms might act locally to protect the functionality of cellular compartments. Indeed, there is evidence that the cytosol [12,13], plasma membrane [14], mitochondria [15], nucleus [16], and ER [17,18] all have dedicated protein QC machineries capable of recognizing and eliminating misfolded or damaged proteins.