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Making and breaking the inner nuclear membrane proteome

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Abstract

The nuclear envelope (NE) is the defining feature of eukaryotic cells, separating the nucleus from the cytoplasm. It has a complex architecture consisting of two lipid bilayers that, despite being continuous between them and with the endoplasmic reticulum, have different protein compositions consistent with their distinct functions. In particular, the unique composition of the inner nuclear membrane (INM), facing the nucleoplasm and its underlying nuclear lamina, is critical for the organisation and function of nuclear processes, from cell fate to gene regulation and DNA repair. Mutations in INM proteins affecting this organisation are associated with muscular dystrophies and premature ageing syndromes highlighting the role of INM architecture in cell homeostasis. Here, we discuss recent progress in understanding how specific proteins concentrate at the INM, as well as the quality control mechanisms involved in remodelling and maintaining INM protein homeostasis.

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Introduction

The endoplasmic reticulum (ER) consists of an extended network of tubules and cisternae bound by a continuous membrane defining a single luminal space. Despite its continuity, the ER membrane is organised in domains of distinct morphology and composition, allowing this organelle to carry out a multitude of functions. For example, ribosome studded sheet-like ER cisternae are predominantly involved in the biogenesis of most secretory and membrane proteins. In contrast, dynamic and branched ER tubules project throughout the cytoplasm establishing contacts with all other cellular organelles and influencing several aspects of their behaviour, such as position or division. The ER is also critical in lipid biosynthesis and regulation of calcium levels, but how these functions are spatially organised within the ER is unclear.

However, the most specialised ER domain is the inner nuclear membrane (INM), which together with the outer nuclear membrane (ONM), forms the nuclear envelope (NE) that separates the cytoplasm from the nucleoplasm. The INM has important and varied roles in nuclear organisation and architecture. As an anchor point for chromosomes at the periphery of the nucleus, the INM organises chromosome spatial distribution, thereby influencing gene expression during development and in differentiated cells [1]. The INM role in chromatin positioning has also been implicated in DNA replication, recombination and repair [2]. Additionally, the INM also regulates the positioning and movement of the nucleus, impacting processes such as cell migration, asymmetric cell division and tissue architecture [3]. To accomplish these diverse functions, the INM relies on a set of proteins that is distinct from the one found in other ER domains. Importantly, mutations in INM proteins have been linked to a wide range of diseases such as muscular dystrophies, progeroid syndromes and cancer highlighting the critical role of the INM proteome [4–6]. Here, we discuss recent progress in understanding how the INM protein identity is established and maintained, with a particular focus on protein quality control processes.

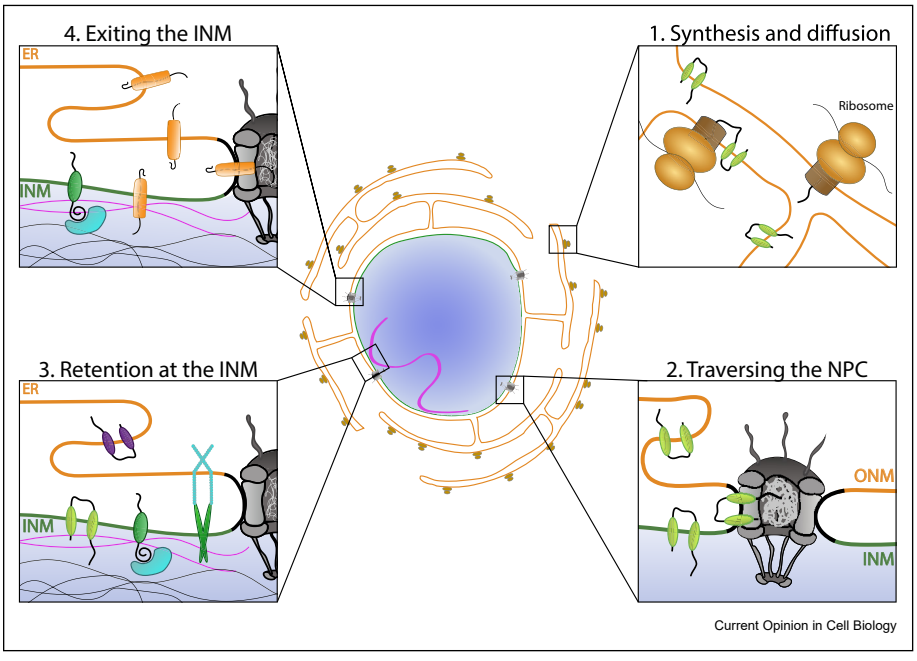
Building a specialised ER domain – Protein targeting to the inner nuclear membrane

Like other ER membrane proteins, the biogenesis of INM-specific proteins occurs in the ER regions facing the cytoplasm. However, upon synthesis, they segregate from the bulk ER to concentrate specifically at the INM. The trafficking of proteins to the INM has been analysed in different cell systems, and the prevailing model suggests that most proteins concentrate at the INM via a diffusion-retention mechanism [7,8]

(Figure 1). According to this model, newly synthesized proteins explore the ER membrane by diffusion. Proteins that reach the INM and are capable of interacting with nuclear components, such as lamins, DNA or chromatin-associated proteins, are retained, resulting in their concentration at the INM [9]. On the other hand, proteins lacking affinity for nuclear components diffuse out and fail to concentrate at the INM. Indeed, microscopy-based screening showed that a large fraction of ER membrane proteins traffics through the INM [10].

A recent study showed that the diffusion of membrane proteins to the INM is largely influenced by the connectivity and dynamics of the ER network. The depletion of the ER-bound GTPase atlastin, essential for ER network connectivity by promoting homotypic fusion of ER membranes, resulted in diminished trafficking of INM proteins. Together with mathematical modelling, this data indicates that changes in the interconnection of the ER network are a major determinant for the diffusion and targeting of proteins to the INM [11]. Another important determinant affecting protein trafficking to the INM is the size of their nucleoplasmic domains. On their way to the INM, membrane proteins traffic via the pore membrane, which links the ONM and INM. Pore membrane displays high curvature, which per se may disfavour the traffic of certain proteins, for example, due to the presence of many transmembrane domains. In addition, the pore membrane houses the nuclear pore complexes (NPCs), through which molecules traffic in and out of the nucleus. However, instead of the NPC central channel used by soluble proteins, most membrane proteins are thought to traffic via narrow NPC peripheral channels (~10 nm diameter) observed by cryo-EM tomography [12]. Owing to their size, these channels can only accommodate globular domains of up to approximately 60 kDa [12,13]. Recent studies in mammalian tissue culture cells using state-of-the-art single-molecule live-cell imaging approaches further supported the hypothesis that the size of cytoplasmic/nucleoplasmic domains of membrane proteins can act as a selectivity filter in protein trafficking to the INM [7,8,14]. Intriguingly, some proteins could avoid the size restriction of the cytoplasmic/nucleoplasmic domain. This behaviour was dependent on the presence of an intrinsically disordered region and a nuclear localisation signal in their cytoplasmic domain, which allows them to make use of both the peripheral and the central NPC channels [13,15]. Interestingly, the targeting of some yeast proteins to the INM depends on similar determinants [16]. Yet, while the diffusion-retention model explains the enrichment of most INM proteins analysed so far, alternative mechanisms, some reminiscent of the direct transport used for nuclear import of soluble proteins, also appear to exist [17]. Given the high number of INM resident proteins and their importance in NE homeostasis, it is not surprising that multiple targeting mechanisms evolved.

Figure 1



The diffusion-retention model for INM protein targeting. Upon their synthesis by ribosomes in the cytoplasmic ER, membrane proteins diffuse in the plane of the membrane (1). Once they reach an NPC, proteins with extramembrane domains smaller than ~60 kDa diffuse via the pore membrane into the INM (2). Interaction with nuclear components results in the retention of proteins at the INM (3). Proteins without affinity to nuclear components will diffuse back into the cytoplasmic ER (4).

In most eukaryotic cells, such as mammalian cells, the unique organisation of the INM is lost during cell division, which requires the disassembly of the NE. This process is driven by the phosphorylation of NE components by mitotic kinases and leads to the dispersal of INM proteins throughout the ER membrane. After chromosome segregation, the reversal of mitotic phosphorylation leads to a fast reassembly of the NE including the reestablishment of INM organisation. These processes are discussed in detail in several excellent reviews [18–23].

Quality control of the INM proteome by the ubiquitin-proteasome system

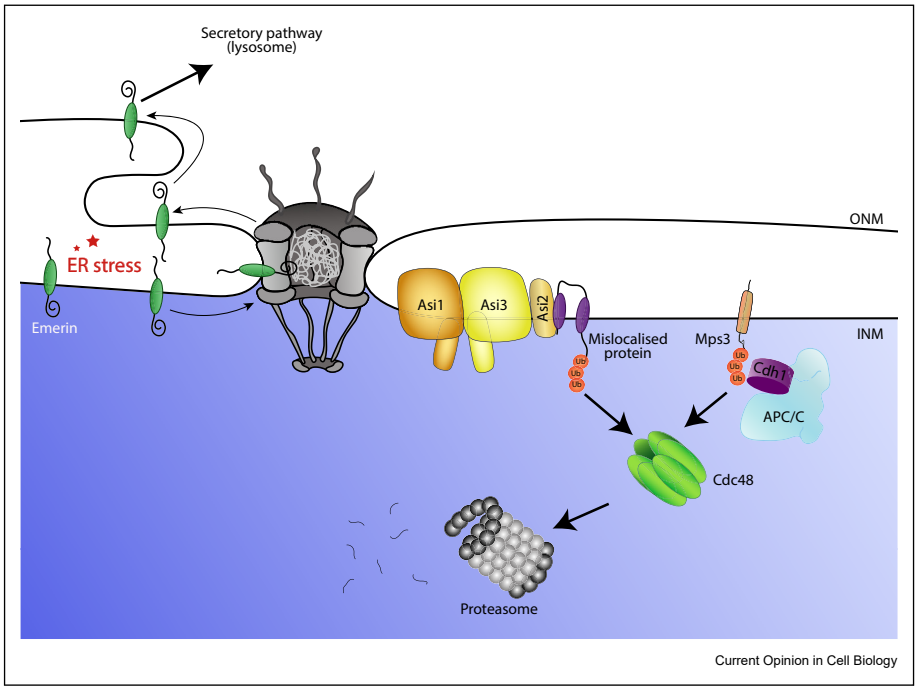
Besides protein targeting mechanisms, selective protein degradation also contributes to the maintenance of INM proteome identity. Recent studies, primarily in budding yeast, showed that both proteasome and lysosome-dependent processes are important in preserving INM protein homeostasis and a functional INM.

The process by which proteins are selectively removed from the INM and targeted for degradation by nuclear proteasomes was coined INM-associated degradation (INMAD). Similar to ER-associated degradation (ERAD) in ER membranes exposed to the cytosol [24], INMAD is mediated by membrane-bound ubiquitin ligase complexes, which selectively recognise and ubiquitinate substrate proteins at the INM. Ubiquitinated substrates are subsequently translocated from the INM into the nucleoplasm (a step known as retrotranslocation) with the aid of the soluble Cdc48 ATPase complex and handed to the proteasome for degradation.

The yeast Amino acid signalling-independent (Asi) complex, consisting of the Asi1/Asi3 ubiquitin ligases and the substrate adaptor Asi2, plays an important role in INMAD by primarily targeting proteins that mislocalised to the INM [25,26] (Figure 2). Mutations in Asi complex components result in the accumulation of mislocalised proteins at the INM, which in some circumstances become toxic. Among Asi substrates are unassembled subunits of protein complexes, suggesting that orphaned proteins reach the INM more readily, whereas if assembled with the partners in larger complexes, those proteins are mostly excluded from the INM [27]. These observations suggest that INM protein quality control also contributes to maintaining subunits of protein complexes within near-stoichiometric levels.

Mechanistically, Asi2 binds directly to the transmembrane segments of some mislocalised proteins, facilitating their ubiquitination by the Asi1/Asi3 ubiquitin ligase. *In vitro* reconstitution experiments suggest that the Asi complex, aided by the Cdc48 ATPase, also

Figure 2



Modes of selective protein degradation from the INM. Upon ER stress, the INM protein Emerin relocalises to the cytoplasmic ER and traffics via the secretory pathway to the lysosome for degradation (left). Proteins at the INM are degraded by INMAD (centre and right). Membrane proteins mislocalised to the INM are recognised by the Asi ubiquitin ligase complex. Upon ubiquitination, mislocalised proteins are pulled into the nucleoplasm with the help of soluble Cdc48 ATPase complex and handed to the proteasome for degradation (centre). The INM protein Mps3 is degraded by an analogous process involving the soluble ubiquitin ligase APC/C^{Cdh1} (right).

promotes the retrotranslocation of its membrane substrates [27]. Consistently, it was shown that protein retrotranslocation from the INM occurs independently of Dfm1, an ER protein implicated in the retrotranslocation of membrane proteins during ERAD [28]. Some substrates are targeted independently of Asi2, suggesting that multiple substrate selection mechanisms are employed by the Asi complex. How Asi2-independent substrates are recognised is not yet clear.

Besides the degradation of mislocalised proteins, the Asi complex also controls other aspects of INM protein homeostasis, such as protein distribution [29]. This is the case with Pom33, a membrane-bound NPC component. Instead of the normal uniform INM distribution, Asi mutant cells display aberrant Pom33 foci along the INM without affecting overall Pom33 abundance. It appears that the Asi complex facilitates Pom33 distribution by promoting its monoubiquitination. Nup188 and Nup120 nucleoporins also colocalise with Pom 33 foci in the absence of Asi, while the distribution of other NPC components and various INM proteins is unaffected in Asi mutants, suggesting that monoubiquitinated Pom33 functions outside the NPC.

Another ubiquitin ligase involved in INM protein degradation is Doa10 [30]. In contrast to the Asi complex, which is restricted to the INM, Doa10 localises throughout the ER and also plays a well-established role in ERAD [30–33]. In fact, the only Doa10 INM substrate described so far is the Asi complex subunit Asi2 [34]. It will be interesting to investigate if Doa10-dependent degradation of Asi2 has a regulatory role in INMAD and whether it has additional INM substrates.

The INM protein Mps3, involved in spindle pole formation and telomere maintenance [35], is also targeted by INMAD. Curiously, its degradation is independent of both Asi and Doa10 ubiquitin ligases. Instead, Mps3 degradation depends on a soluble ubiquitin ligase, the anaphase-promoting complex/cyclosome (APC/C). Mutations in APC/C or its activator Cdh1 result in the Mps3 accumulation [36], and the overexpression of non-degradable Mps3 is toxic to cells, underscoring the importance of Mps3-regulated degradation. Consistent with the involvement of a soluble ubiquitin ligase, Mps3 degradation depends on motifs in its nucleoplasmic domain and appears to be regulated through phosphorylation by a yet-to-be-identified kinase. In addition to a nucleoplasmic regulatory region and a single transmembrane segment, Mps3 contains a large domain in the ER lumen. Thus, its retrotranslocation and membrane extraction likely requires assistance, but the factors involved in this process have not been identified.

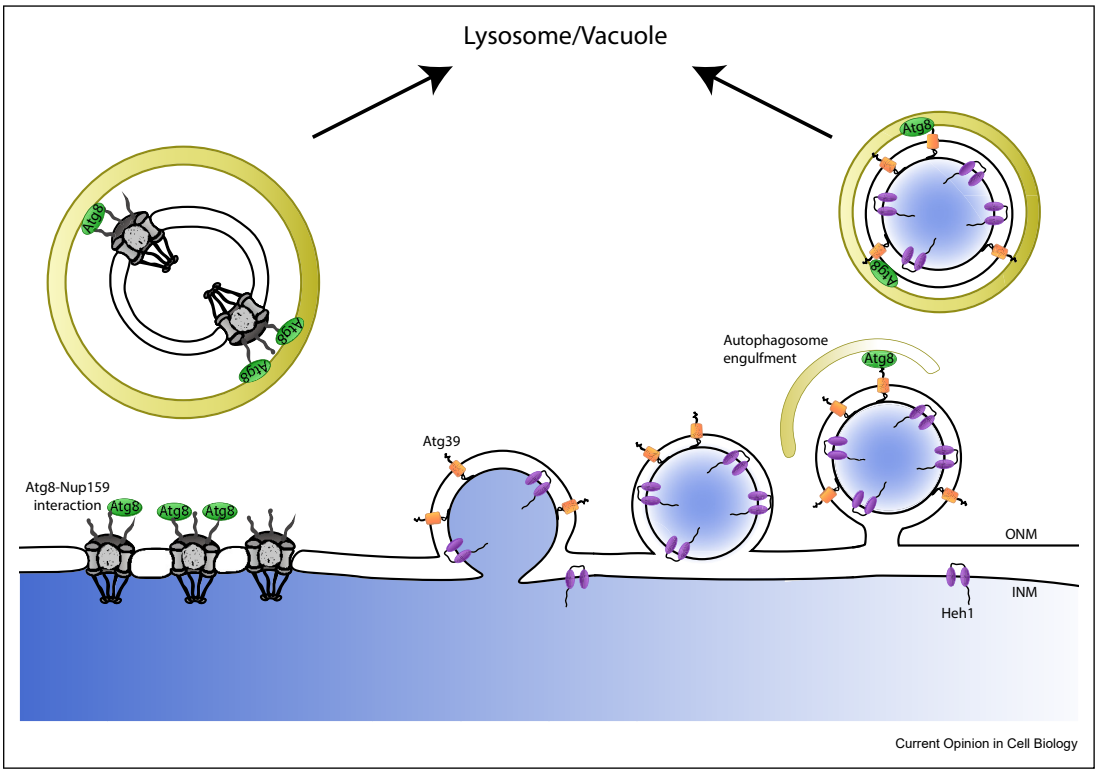
In mammalian cells, our knowledge of INMAD is rudimentary even if the turnover of INM proteins occurs at similar rates as for proteins in other ER domains, as shown by recent proteomics studies in C2C12 myoblasts [37]. Among the few INM proteins analysed is the Mps3 homologue SUN2, which appears to be a substrate of the soluble Skp1/Cullin1/F-box/βTRCP ($SCF^{\beta TRCP}$) ubiquitin ligase. Proximity-biotinylation experiments identified SUN2 as a $SCF^{\beta TRCP}$ partner, and the depletion of $SCF^{\beta TRCP}$ resulted in the accumulation of overexpressed SUN2 at the INM [38]. While preliminary, these findings show intriguing similarities with the APC/C-dependent degradation of Mps3 in yeast, suggesting a more general role of soluble ubiquitin ligases in shaping the INM proteome.

The turnover of Lamin B receptor (LBR), another prototypical INM protein, has also been analysed. While wild-type LBR is normally long-lived, disease-associated LBR mutants are rapidly degraded by INMAD, though the machinery responsible for its degradation is unknown [39]. Similarly, mutations on the INM protein Emerin also result in its degradation by an INMAD-like process [37]. Surprisingly, under ER stress, a fraction of mutant Emerin is degraded in lysosomes. Live-cell imaging experiments showed that acute ER stress by calcium depletion triggers Emerin to leave the INM and traffic to the lysosome via the secretory pathway [37] (Fig. 2). How the mutant versions of LBR, Emerin and likely other aberrant INM proteins are selectively recognised and targeted for degradation are important open questions. Moreover, the determinants routing substrates to INMAD for degradation by the proteasome or promoting their traffic to the lysosome remain elusive.

Autophagy-dependent protein degradation at the INM

Autophagy was also shown to play a role in INM homeostasis. However, in contrast to INMAD, where single protein molecules are cherry-picked for degradation, autophagy promotes the degradation of large NE protein assemblies, such as NPCs, or even entire regions of the INM [40–47]. Recent advances in light and electron microscopy (EM) approaches combined with structural analysis *in situ* showed dramatic remodelling of the NE in starved yeast cells [44]. Under these conditions, membrane herniations containing multiple NPCs appear to bud off the NE for autophagic degradation (Figure 3). Direct binding of the nucleoporin Nup159 to the critical autophagy component Atg8 appears to be essential for this process [43]. Interestingly, this process is independent of the autophagy adaptors Atg39 and Atg40, implicated respectively in autophagic turnover of the NE and other ER domains [40,43,45]. The mechanisms by which NE remodelling occurs and the membrane herniations are formed to clear NPCs remain to be determined.

Figure 3



Modes of autophagy-dependent degradation of NE components. Upon starvation, the nucleoporin Nup159 in fully and partly assembled NPCs is bound by Atg8 and subsequently incorporated into autophagosomes for degradation by the lysosome (left). The ONM protein Atg39 interacts with and remodels the INM via AHs in its luminal domain. Atg39-induced membrane remodelling leads to the formation of INM-derived vesicles containing the INM proteins and portions of the nucleoplasm. Through its cytoplasmic domain, Atg39 binds core autophagy components, such as Atg8 resulting in the incorporation of INM-derived vesicles into autophagosomes for degradation by the lysosome (right).

NE remodelling is better understood during Atg39-mediated autophagy [40,41]. Atg39 is a single-pass membrane protein localised at the ONM that uses its N-terminal cytosolic region to interact with cytoplasmic autophagy core machinery, such as Atg8. A framework for selective capture of nuclear cargo by Atg39 was recently proposed, whereby the extended C-terminal region reaches out across the ER lumen and interacts with the INM [40,46]. This interaction with the INM is mediated by a pair of amphipathic helices (AHs) in the Atg39 luminal region. These AHs are important to restrict Atg39 localisation to the NE, as well as to induce membrane curvature and ultimately trigger the formation of INM-derived vesicles (Figure 3). The overexpression of Atg39 in cells defective for late autophagy steps results in the accumulation of INM-derived vesicles, suggesting that they are an intermediate step in nucleophagy. Importantly, deleting or swapping Atg39 AHs with an amphipathic lipid packaging sensor (ALPS) motif precluded INM-derived vesicle formation. Understanding how the AHs of Atg39 specifically target and deform the INM is an important unresolved issue. INM-derived vesicles were shown to contain Heh1 and Tal1, an INM and nucleoplasmic protein, respectively, but not components of the NPC. A systematic analysis of the INM-derived vesicle content is still missing, but it may provide clues about the physiological relevance of Atg39-mediated nucleophagy in INM homeostasis.

In mammalian cells, Lamin B, a nuclear lamina protein, is also turned over by autophagy. However, in contrast to yeast cells, NE remodelling in mammalian cells is not triggered by starvation but instead by the expression of an oncogenic mutation of the RAS small GTPase [47]. Experiments in primary human cells suggest that Lamin B degradation by autophagy has a tumour suppressor role. Whether other physiological conditions also trigger autophagy of Lamin B or other NE components remains unknown. Mammalian cells have no obvious homologue of yeast Atg39. Thus, another important open question is the identity of the autophagy adaptors at the mammalian NE.

The last few years were important in establishing the dynamic nature of the INM proteome. However, we expect the years to come to bring many more important

insights into the mechanisms controlling protein homeostasis at the INM and how these impact cell physiology.

Conflict of interest statement

Nothing declared.

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