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Lamins and Lamin-Associated Proteins in Gastrointestinal Health and Disease

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The nuclear lamina is a multi-protein lattice composed of A- and B-type lamins and their associated proteins. This protein lattice associates with heterochromatin and integral inner nuclear membrane proteins, providing links among the genome, nucleoskeleton, and cytoskeleton. In the 1990s, mutations in *EMD* and *LMNA* were linked to Emery-Dreifuss muscular dystrophy. Since then, the number of diseases attributed to nuclear lamina defects, including laminopathies and other disorders, has increased to include more than 20 distinct genetic syndromes. Studies of patients and mouse genetic models have pointed to important roles for lamins and their associated proteins in the function of gastrointestinal organs, including liver and pancreas. We review the interactions and functions of the lamina in relation to the nuclear envelope and genome, the ways in which its dysfunction is thought to contribute to human disease, and possible avenues for targeted therapies.

Keywords: Nucleoskeleton; Envelopathies; Progeria; Myopathy; Neuropathy; Lipodystrophy; Nonalcoholic Fatty Liver Disease.

In metazoan cells, a structural and functional link between the genome and the cytoskeleton is required to allow cells to quickly and appropriately respond to mechanical, chemical, inflammatory, and other stimuli. This link is provided by nuclear envelope proteins, which have collective and individual structural and regulatory roles. Nuclear pore complexes allow regulated nuclear translocation of transcription factors and co-regulators.[1] The linker of the nucleoskeleton and cytoskeleton (LINC) complex tethers the nuclear envelope to cytoplasmic cytoskeletal networks, allowing transmission of mechanical and shear stress to the nucleus.[2] On the inner surface of the nuclear envelope, large regions of the genome, typically dominated by heterochromatin, are tethered to a multi-protein lattice[3,4] (Figure 1). This complex of proteins, the nuclear lamina, lies beneath the inner nuclear membrane and physically associates with nuclear pore proteins and a variety of transmembrane and integral membrane proteins, and is in direct contact with large portions of the genome.

The primary components of the nuclear lamina are lamins, which are type V intermediate filament proteins—the most common intermediate filament proteins in the nucleus (although other intermediate filament proteins, such as keratins, are also found at much lower levels in the nucleus).[5–8] Lamins are encoded by 3 genes that generate the proteins: lamin A/C (*LMNA*; protein also referred to as LMNA), lamin B1 (*LMNB1*; protein also referred to as LMNB1), and lamin B2 (*LMNB2*; protein also referred to as LMNB2).[9–11] The B-type lamins are expressed ubiquitously and throughout development, whereas A-type lamins are primarily expressed in differentiated cells.[12,13] Together these proteins form a lattice that creates an interface with the inner nuclear membrane, nuclear pore complexes, transcription factors and co-regulatory proteins, and chromatin. Anchoring of the lamina to the inner nuclear membrane is achieved via B-type lamin farnesylation and lamin binding to transmembrane proteins that include lamina-associated polypeptide 1 and LEM-domain containing proteins, such as LAP2β, emerin, and MAN1 (also called LEMD3),[14] whereas anchoring to the genome is thought to occur via adaptor proteins, including barrier to autointegration factor (BANF1), the lamin B receptor (LBR), and direct binding of lamins to chromatin.[15–18]

Lamin Post-Translational Processing and Localization

Lamin C does not require post-translational modification to localize to the inner nuclear membrane. Lamin A, however, requires stepwise post-translational processing at the carboxy terminus via cysteine farnesylation at a cysteine–aliphatic–aliphatic–any amino acid (CAAX) motif, then

Abbreviations used in this paper: **BANF1, barrier to autointegration factor; EDMD, Emery-Dreifuss muscular dystrophy; FTI, farnesyl transferase inhibitor; FPLD2, type 2 (Dunnigan) familial partial lipodystrophy; HCC, hepatocellular carcinoma; HGPS, Hutchinson–Gilford progeria syndrome; LAD, lamina-associated domain; LAP, lamina-associated polypeptide; LBR, lamin B receptor; LINC, linker of the nucleoskeleton and cytoskeleton; LMNA, lamin A/C; LMNB1, lamin B1; LMNB2, lamin B2; mRNA, messenger RNA; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; RB1, RB transcriptional corepressor 1.**

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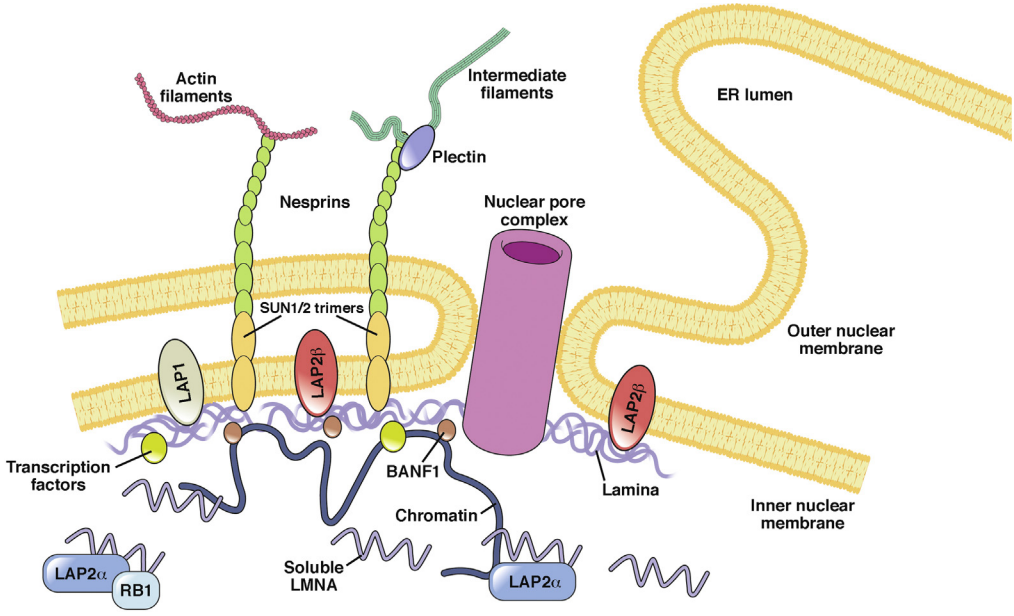

Figure 1. Schematic of the nuclear envelope structure including outer and inner nuclear membranes, the lamina, integral membrane proteins, nuclear pore complex, LINC complexes, components of the cytoplasmic cytoskeleton, and chromatin-lamina contacts. The outer nuclear membrane is shown in continuity with the membrane of the endoplasmic reticulum (ER). A portion of LMNA is shown as a soluble nucleoplasmic protein, some of which is bound to LAP2α.

proteolytic cleavage of the –AAX portion, carboxymethylation of the farnesylcysteine, and final clipping of the 15 carboxy-terminal residues, including the farnesylated cysteine, by the zinc metallopeptidase STE24 (ZMPSTE24).[19–22] Although the B-type lamins are permanently farnesylated and found exclusively at the inner nuclear membrane as part of the nuclear lamina, a portion of LMNA is found in the nucleoplasm. Nucleoplasmic LMNA is stabilized by a mammal-specific isoform of thymopoietin (TMPO or LAP2), called LAP2α, but little is known about its function.[23,24]

Lamina-Associated Proteins

A- and B-type lamins form an intricate network of overlapping but independent 3-dimensional protein meshes[25] that interact with distinct subsets of the nuclear proteome. Lamin interactors include transmembrane LEM domain proteins, such as LAP2β and MAN1; transcription factors such as SREBP1; transcriptional regulators, including RB transcriptional corepressor 1 (RB1); and adaptor proteins, such as BANF1, that might facilitate chromatin binding to the lamina.[15,17,26,27] Two other critical nuclear envelope structures mediate interactions between the nucleus and cytoplasm: nuclear pore complexes and the LINC complex. Nuclear pore complexes allow transcription factors, nuclear receptors, and signaling proteins to shuttle between the nucleus and cytoplasm.[1] A subset of nuclear pore complex proteins localizes to the nuclear periphery and/or with inactive regions of heterochromatin, whereas others are associated with active areas of euchromatin in the nuclear interior.[28–30] How this is regulated, and whether lamins or adaptor proteins such as BANF1 are involved, is unclear. Finally, the LINC complex[2] forms a key structural and regulatory connection between the nuclear envelope and the cytoskeleton, binding to nuclear lamins and the inner nuclear membrane on one side and actin filaments on the other (Figure 1).

Lamina–Heterochromatin Interactions and Lamina-Associated Domains

Several landmark studies have demonstrated the physical association between large regions of the genome (typically characterized by heterochromatin) and the nuclear lamina.[3,31–34] Some genomic regions—usually gene-poor, transcriptionally inactive regions—are associated with the lamina as part of lamina-associated domains (LADs) in numerous cell types, including pluripotent and terminally differentiated cells. In contrast, other regions of the genome may be found within or outside of LADs, depending on the cell type, or may move in and out of LADs during the process of cellular differentiation.[3,35] For example, genomic regions associated with the lamina and transcriptionally silent in embryonic stem cells were found to dissociate from the lamina and become transcriptionally active during astrocyte differentiation.[31] Association with or dissociation from the nuclear lamina is therefore an important mechanism of transcriptional regulation during development; differential histone post-translational modification (methylation/acetylation) is likely to be involved in this process. Importantly, few studies have explored how disease-associated lamin variants affect organization of the genome and the LAD landscape in the involved tissues.[36]

Lamina-Related Diseases

Researchers began to realize that alterations in the nuclear lamina can lead to development of disease when genetic mapping and sequencing became widely available in the 1990s. In 1994, mutations in *EMD*, encoding emerin, an inner nuclear membrane protein, were found to cause X-linked Emery–Dreifuss muscular dystrophy (EDMD).[37] Subsequently, autosomal mutations in *LMNA* were found to cause EDMD.[38] In the following years, many