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Understanding Lamin Proteins and Their Roles in Aging and Cardiovascular Diseases

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Word Count: 6200

Figure Count: 2

This is the author's manuscript of the article published in final edited form as:

Jiang, Y., & Ji, J. Y. (2018). Understanding lamin proteins and their roles in aging and cardiovascular diseases. Life Sciences. https://doi.org/10.1016/j.lfs.2018.09.026

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Abstract

The occurrence of cardiovascular diseases increases with age independent of other risk factors, and the percentage of senescent cells is significantly elevated in vascular cells at atherosclerotic sites. Patients with accelerated aging syndromes caused by mutant lamin A protein, a structural component in nuclear lamina, also share many similarities with normal aged people, including the propensity to develop atherosclerosis. Recent studies have revealed the accumulation of prelamin A in normal aged vascular cells, and that lamin A participated as a mechanosensitive molecule in regulating various cellular events. These findings suggest that the ectopic expression of mutant lamin A or lamin A precursor (prelamin A) not only causes defects in cell mechanics, but it also disturbs stress-induced mechanotransduction pathways involving lamin A, both of which may contribute to vascular dysregulation. This review summarizes the current understanding of how lamin proteins are involved in vascular cell during aging, with a particular focus on the effect of mechanical stresses from blood flow on nuclear lamina of endothelial cells. Related studies are clarifying the role of lamin A in the progression of atherosclerosis, which will aid in the development of potential therapies for those suffering from lamin A-associated accelerated aging syndromes.

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Keywords: lamins, laminopathies, progerin, vascular aging, atherosclerosis

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1. Introduction

Cardiovascular disease (CVD) is among the leading causes of death in the United States [3]. The progression of CVD often initiates on the endothelium, which generally acts as the first barrier to separate pulsatile blood flow and the interstitium, and at the same time provides semi-permeability for solutes and fluids to establish vascular homeostasis [4-6]. Many vascular risk factors, such as hypercholesterolemia, hypertension and aging were found to disturb endothelial functions by activating endothelium, and that activation will promote the recruitment and differentiation of circulating monocytes at the local area, which is followed by smooth muscle cells (SMC) proliferation due to altered cell-cell communications. These cellular events accompanied with the overproduction of extracellular matrix (ECM) together accelerate the atheromatous plaque buildup [7]. This disease progression is known as atherosclerosis, and the plaque rupture can cause severe thrombosis and even death in cases such as stroke or heart attack [8].

Vascular cells experience mechanical stimuli (tangential shear stress and circumferential strain) that are generated by the pulsatile blood flow *in vivo,* as shown in Figure 1 [9]. These mechanical cues also play an important role in the progression of atherosclerosis. Previous studies have shown that the atherosclerosis formation sites are structure-specific, preferentially occurring at arterial curvatures and branching points. At these sites vascular cells experience oscillatory and low shear stress and increased cyclic strain [10-13]. These mechanical forces have been shown to constantly regulate vascular physiology and pathology. In endothelial cells, the actin stress fibers aligned along the direction of minimum substrate deformation, for example the direction oblique to applied uniaxial stretch *in vitro* [14-19], probably through the activation of RhoA by Rho-guanine nucleotide exchange factors (Rho-GEF) [20]. After exposure to regular shear stress, the filaments reoriented along the flow direction in concomitance with remodeling of cell-substrate adhesion and cell-cell adherent junctions [21]. The combination of these two physiological mechanical forces can also produce a synergistic effect on actin remodeling patterns [22]. Moreover, the angle between the flow and cell axis could have differential effects on the activation of endothelial nitric oxide synthase (eNOS) and NF-κB (a proinflammatory transcription factor). These findings suggest the capacity of hemodynamic forces on remodeling the

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endothelial morphology in a force pattern dependent manner [23]. Selective gene expression and biochemical production in vascular cells can also be altered by distinct patterns of mechanical forces [24-27]. Endothelial microRNAs (miRNAs) expression profile that is critical in regulating diverse cell events, including cell apoptosis and proliferation, was shown to depend on the shear stress pattern [28,29]. The production of endothelin-1, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin and NOS activity were also sensitive to shear pattern [14-16,18,19,30-32]**.** It is recently reported that the endothelial sensitivity to the flow can be regulated by non-canonical Wnt signaling [33]. Also, endothelial cells from different species or vascular beds can elicit differential oxidative responses and gene expression profiles toward mechanical forces [34-36]: Sung et al. reported that human aortic endothelial cells (HAEC) were more susceptible to fluid agitation, while HUVECs were more sensitive to cyclic strain in terms of the productions of reactive oxygen species (ROS) and cell adhesion molecules. These findings suggest that distinct mechanotransduction responses may exist in cells from different vascular origins [37].

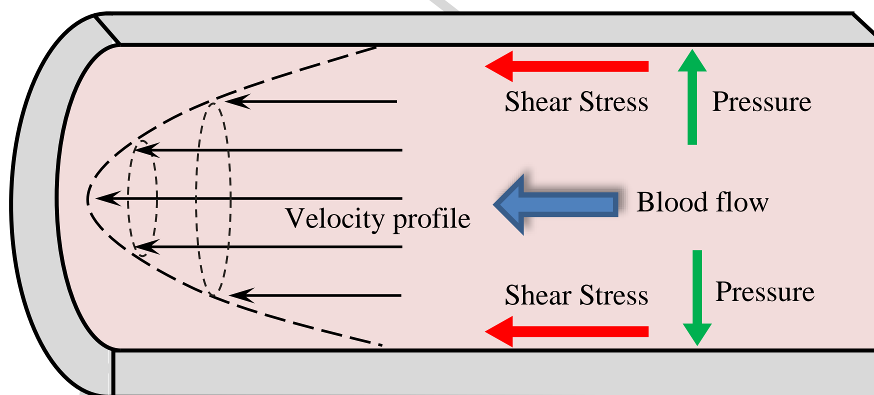

Figure 1. Illustrative image of main hemodynamic forces exerted on vascular wall. The viscous characteristic of blood flow induces non-uniform velocity profile within the blood vessel, which leads to the creation of shear stress parallel to the blood flow direction. The pulsatile blood flow also induces pressure changes onto the vessel wall [2], which on the other hand causes blood vessels to stretch circumferentially. Arrows denote the directions of blood flow and mechanical forces. Shear stress is tangential to vessel wall, while pressure is perpendicular.

The nucleus also plays a significant role in the mechanotransduction pathways by nucleo-cytoskeletal coupling via Linker of Nucleoskeleton and Cytoskeleton (LINC) complex [38], a mechano-responsive protein complex associated within nuclear envelope, which contains SUN-domain proteins (SUN1 and 2) and KASH-domain proteins (Nesprin 1, 2, and 3) that bind to nuclear lamina and

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cytoskeleton, respectively [39]. Endogenous and exogenous forces as mechanical stimuli can trigger structural and compositional changes in nuclear envelope, and modulate gene expression and cell behaviors by activating many downstream regulators [40-42].

The integrity of nucleus is largely supported by nuclear lamina, a dynamic network that sits underneath the inner nuclear membrane composed of lamin polymers and lamin-associated proteins [43]. As the main contributor to nuclear mechanical properties, the lamina is crucial in preventing DNA damage during nuclear deformation and cell migration [44,45], and its proximity to heterochromatin also enables its role in stabilizing spatial organization of genome [46]. It helps transfer forces to the tethered chromatin via coupling with LINC complex, and responds to changes in the ECM by mediating lamins expression, in a manner that helps maintain nuclear stiffness in various tissues [47,48]. The nuclear lamina is involved in various cellular events that determine cell fate, and defects in the lamina contribute to disease phenotypes and impaired mechanotransduction pathways.

Lamins are type V intermediate filament (IF) proteins recognized as a filamentous network at first glance [49]. Besides acting as a structural support for nuclei under mechanical stresses, lamins were also found to participate in DNA replication and repair, as well as in gene regulations through interactions with peripheral heterochromatins or mechanosensitive transcription factors (TFs) [50-53]. Recent findings have indicated correlations between mutated lamin forms and atherosclerosis during aging process, suggesting that lamin proteins may play a role in the development of atherosclerosis particularly during normal aging [54-56].

The lamins are classified into two subgroups in vertebrates: A-type lamins (encoded by LMNA gene) and B-type lamins (encoded by LMNB1 or LMNB2 gene) by different isoelectric values [57,58]. They both have the protein structures and domain interactions typical of intermediate filaments, and further associations of these lamin polymers eventually generate filaments with 10 nm in diameter *in vitro* [59-61]. Although evidence showed that A- and B-type lamins form distinct but interacting network in mammalian cells [62], the *in vivo* organization of lamins filaments remains unknown, and it is considered to be more heterogeneous than the observed woven-like network in Xenopus *laevis* oocyte, which only

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has B-type lamins [61]. Recent application of cryo-electron tomography (cryo-ET) on the lamina revealed its supramolecular organization: a 3.5 nm thick lamin filament meshwork with globular structures that represent the immunoglobulin-fold domains [63].

Within the lamin family, lamin A and lamin C are two major forms originated from LMNA gene by alternative splicing, and lamin B1 and lamin B2 are generated from LMNB1 and LMNB2, respectively [64]. All major lamins except lamin C possess a CAAX motif at the carboxyl-terminus after protein synthesis where the cysteine (C) is farnesylated by farnesyltransferase (FT) to facilitate the protein localization at the nuclear envelope (NE). After that, the aaX residues are hydrolyzed by farnesylated proteins-converting enzyme 2 (FACE2) on lamin B1 and B2, or by a zinc metallo-endoprotease (Zmpste24 or FACE-1) on prelamin A (the precursor for lamin A). The farnesylated cysteine at the end will be methylated afterwards, and all those steps will lead to the permanently farnesylated tails on B-type lamins. However, the additional removal of the last 15 amino acids (including the farnesylated cysteine) by Zmpste24 will occur on lamin A precursor before it proceeds to mature lamin A (Figure 2) [65].

Aside from the slight differences in post-translational steps, A- and B-type lamins were also found to perform differently in multiple cellular events. During mitosis, the nuclear lamina undergo disassembly, where A-type lamins diffused into the nucleoplasm at early prophase, while B-type lamins tended to be fragmented and concentrated near the mitotic spindle later during metaphase [66]. The reassembly timing for them also differed, indicating their diverse disassembly and reassembly mechanisms during cell division [67]. Furthermore, contributions of these lamins to nucleus mechanics are also distinct. While the ablation of lamin A/C or lamin A resulted in a compromised nuclear shape and stiffness in fibroblasts, lamin B1-deficient cells had more nuclear blebs (membrane invaginations and protrusions) without discernible alternations in nuclear mechanics [68]. This discrepancy may be due to greater association and stabilization between A-type lamins and nuclear structural proteins, such as emerin, nesprins, and lamina-associated polypeptide 2 isoform alpha (LAP2α) [69-71].

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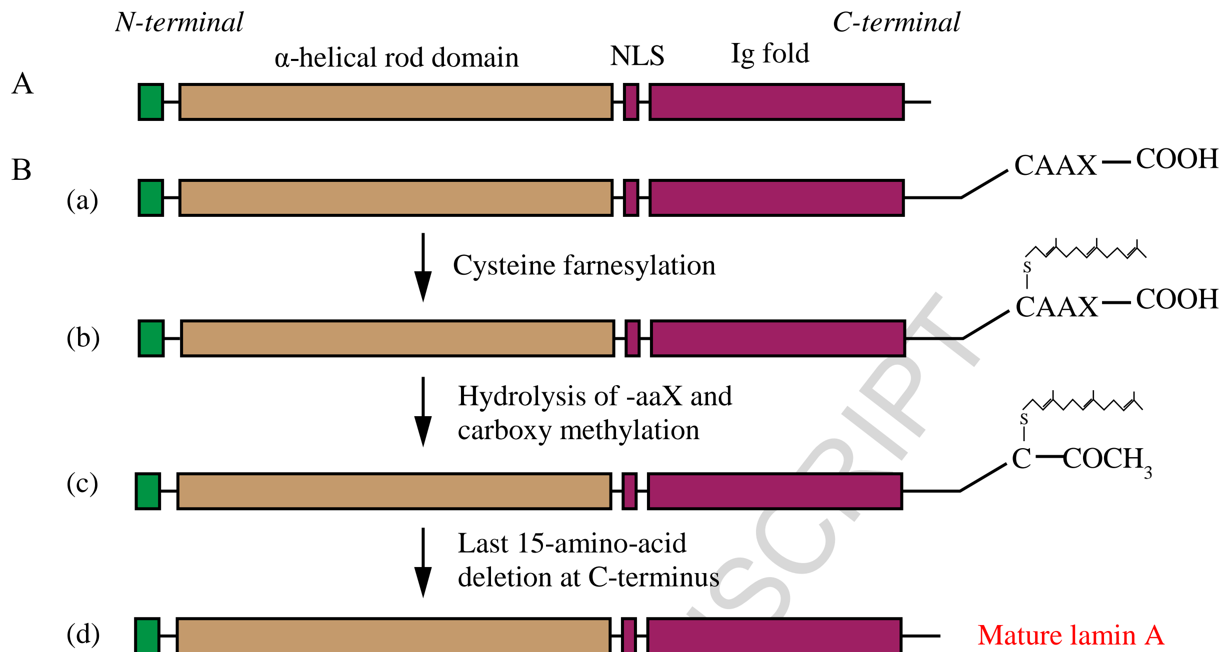

Figure 2. Schematic drawing of typical lamins structures **(A)**, including a highly conserved α-helix rod domain and a more divergent N-terminal head and a C-terminal tail that contains NLS (nuclear localization signal that contains chromatin binding site) and Ig fold domain [1]. **(B)** Post-translational modifications in lamin proteins. Lamins after protein synthesis contain a complete –CAAX motif at C-terminus (a), and the cysteine in –CAAX motif is farnesylated by farnesyltransferase (b). The aaX residues are removed and the cysteine at the C-terminus is methylated (c). Mature lamin A will be generated after the last 15 amino acids being removed by ZMPSTE24 (a zinc metallo-endoprotease) (d).

In the past decades, more than 17 diseases have been reported to be associated with lamin gene mutations (mainly LMNA gene), and they are collectively named laminopathies [50]. Mutations involving LMNB1 and LMNB2 genes mostly cause disorders in neural development and degeneration, such as adult-onset autosomal dominant leukodystrophy (ADLD) and are often lethal [72-74]. The essential role that B-type lamins play in cell viability might explain the limited quantity of identified mutations in LMNB genes [75]. Conversely, over 500 missense LMNA mutations have been recognized that mainly affected the progeny of mesenchymal stem cells [76,77]. Patients with LMNA mutations often experienced multiple phenotypes, including defects in skeletal and cardiac muscles and loss of subcutaneous adipose tissue, such as in Emery-Dreifuss muscular dystrophy (EDMD) and Dunnigan-type familial partial lipodystrophy (FPLD) [78], as well as peripheral nerve dysfunctions, or disorders resembling aging syndromes in young patients (Hutchinson-Gilford progeria syndrome (HGPS)) [79].

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Notably, the systematic premature aging syndromes (also known as progeroid syndromes) by missense mutations in LMNA, such as Atypical Werner syndrome (WS), Restrictive dermopathy (RD) and HGPS (also called Progeria) have attracted enormous attention given their correlations with the normal aging process. Multiple and overlapping phenotypes were identified in those diseases, including postnatal growth retardation, wrinkled skin, substantial hair loss [80]. While sequencing technique suggested genetic heterogeneity for MAD (Mandibuloacral Dysplasia) and Atypical WS [81], cells from HGPS patients were generally reported to have missense mutations in exon 11 on the LMNA gene. This creates a cryptic splice site responsible for the deletion of 50 amino acids near C-terminus on prelamin A, resulting in an absence of the recognition site for Zmpste24 to remove the final 15-amino-acid at C-terminus. This lack of post-translational modification leads to the generation of a truncated prelamin A called progerin that has a permanently farnesylated tail. RD was reported to have an extra removal of 40 amino acids (totally 90) on prelamin A, which was believed to cause more severe outcomes than HGPS given its lethality in newborns [82,83]. Interestingly, similar phenotypes were also observed in patients or mouse models with mutations or deficiency in Zmpste24 gene [84].

Except for the resemblance in appearance between patients with progeroid syndromes (mainly HGPS) and elderly people, they also shared some similarities at the cellular level, including increased DNA damage, defects in DNA repair and shortened telomere length that significantly impaired cell proliferation capacity [85]. The accumulated DNA damage, as one of the hallmarks of normal aging, was often found in senescent cells [86,87]. Like elderly people, patients with progeriod syndrome were also prone to developing advanced atherosclerotic lesions, but the extensive loss of SMC in arteries and thickened adventitial fibrosis in veins were only observed in HGPS patients [88], and patients with laminopathies of premature aging did not exhibit all normal aging phenotypes [89]. However, the presence of truncated prelamin A in normal aged individuals (at a much lower level) as well as their high genomic instability, telomere attrition, epigenetic and metabolic alternations and cell senescence, particularly in cardiovascular system, still suggest lamin's role in promoting vascular aging [86,90-93]. While B-type lamins, especially lamin B1 were greatly lost in senescent cells [94], their deficiencies were

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recorded to mostly affect nervous system and brain function [72]. However, little evidence has been shown on the role of lamin B with vascular aging or nuclear mechanics [68], and the relationship between B-type lamins and cell senescence remain to be recognized. Related studies might shed more light on the discoveries on aging mechanisms and potential treatments for those patients suffered from accelerated aging diseases [95,96].

2. Roles of lamin A/C in maintaining cell functionality

Lamin A/C serves not only as structural components to support nuclear mechanics, but also interacts with many transcription factors and periphery heterochromatin to regulate gene expression [97,98]. Lamin A/C-associated disorders that affect the vascular system suggest that lamin A/C plays an important role in supporting cell mechanics and in signaling processes under mechanical forces, which may help to understand the underlying mechanisms of atherosclerotic lesion formation process [77,88,99,100].

2.1 Mechanical roles of Lamin A/C

After incorporating into nuclear lamina, lamin A/C forms a filamentous meshwork that modulates the dynamic mechanical properties of nucleus in accordance with the internal and external forces of the cell. This process is achieved not only by the physical connections among ECM, focal adhesions, cytoskeleton and nuclear envelope, but also by many mechanosensitive molecules that were recognized as transducing mechanosignals into nucleus to elicit changes in gene expression profiles [101]. For instance, ECM stiffness was found to be parallel to lamin A/C expression. The resulting post-translational modifications in lamin A/C degradation and phosphorylation via coupling with myosin-IIA can lead to changes in the Serum Response Factor (SRF) pathway, which in turn regulates actomyosin expression [102]. This self-regulating mechanism involving lamin A/C allows cells to respond to its environmental stresses through changes in cell and nuclear mechanics. Since vascular cells exist in a mechanically active microenvironment, it was proposed that lamin A/C is essential in modifying these cells behaviors in response to mechanical forces, and that may partially explain why the absence or mutations in lamin A/C can induce the most abnormalities in cells that are under mechanical loadings [97].

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2.1.1 Lamin A/C Effects on Nuclear Mechanics

Nuclear lamina was proposed to be a natively compressed and elastic network in static state, which can resist potential overloading force to prevent nuclear breakdown [103]. Different types of lamin might contribute to distinct mechanical properties of the nucleus. Observations from micropipette aspiration experiment revealed that B-type lamins contributed more to the nuclear elasticity, while A-type lamins acted to resist nuclear deformation as a viscous network [104,105].

While studies showed that lamin A/C is homogeneously distributed at the nuclear periphery which delineates the nuclear shape, human dermal fibroblasts with silenced or mutated lamin A/C had significant nuclear defects in morphology, such as distorted nuclear periphery and nuclear blebs or invaginations [106]. Increased nuclear deformation was also observed in fibroblasts without lamin A/C present or with lamin mutations that can cause muscular defects. However, fibroblasts from FPLD patients showed normal nuclear stiffness [107]. And in HGPS skin fibroblasts that overexpressed progerin, the stiffness was reported to increase, as well as elevated mechanosensitivity [108]. Those findings are consistent with the varied laminopathy phenotypes by different *de novo* mutations of lamin A/C, indicating that distinct changes in nuclear mechanics can be induced by dissimilar amino acid substitutions on lamin A/C sequence, which could differentially affect the domains or higher order structures on lamin A/C, as well as their filamentous network within the lamina [107,109].

Specifically, the increased nuclear stiffness in HGPS cells might be related to the pathological mechanism of progerin, which tended to aggregate at the nuclear periphery and hamper the deformation of nuclei toward mechanical forces [108,110]. The birefringent orientation of lamins found in HGPS cells may also contribute to the stiffened nuclei [111]. Other than the observed mechanical abnormalities in fibroblasts, the introduction of Δ50 lamin A in HeLa cells also disturbed their morphological responses to laminar shear stress. Similar nuclear defects were also reported in lamin A/C-deficient multinucleated myotubes, indicating the broad effects of lamin A/C on nuclear mechanics regardless of cell types [68,112]. While the treatment of farnesyltransferase inhibitors (FTI) has successfully rescued nuclear shape and the stiffness of HGPS fibroblasts, by removing the farnesylated tail, the cellular

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mechanosensitivity was not ameliorated [108]. Therefore, the recovery of stiffness by releasing progerin into nucleoplasm is not sufficient to help cells to resist external forces.

2.1.2 Lamin A/C Effects on Whole Cell Mechanics

Nuclear lamina has been shown to be associated with cytoplasmic actin filaments, microtubules and intermediate filaments through emerin and LINC complex [46]. Given the fact that the nucleus and cytoplasm are interlinked by physical connections [113], it is not surprising to observe the changes in whole cell mechanical properties when lamin A/C was defective.

The deficiency of lamin A/C in mouse embryonic fibroblasts (MEFs) can lead to softened cytoplasm, compromised viscoelastic properties of the cytoskeleton, decreased cell polarization and migration rate [114,115]. Similar defects were observed in fibroblasts with mutant LMNA ($Lmna^{L530P/L530P}$) that yield HGPS phenotypes in human [116]. These phenomena suggest that the dysfunctional lamin A/C can have adverse effects on cell mechanics. More specifically, silencing lamin A/C can greatly change cytoskeletal structures in MEFs and 3T3 cells, such as disturbed emerin and nesprin-3 localization, depolymerization of actin filaments at perinuclear regions, and abnormal absence or aggregation of vimentin [115]. However, in a mouse model with only lamin C expressed, the targeting of emerin to NE was reported to be normal [117]. This discrepancy might suggest the assistant role of lamin C in helping emerin at nuclear membrane. Mutations in LMNA responsible for muscular dystrophies were found to cause defective actin-dependent nuclear movement, while microtubule-mediated centrosome positioning was not interfered. On the other hand, in $LMNA^{-/-}$ fibroblasts or those with LMNA mutations that cause HGPS or affect adipose tissues, emerin was mislocalized and related to that, disturbed microtubule-dependent cell polarization was observed [115,118]. These findings suggest distinct pathologies of laminopathies with different phenotypes [118].

Overall, evidence has shown that both nuclear and whole cell mechanics were weakened by mutated or deficient lamin A/C with dysfunctions in various structural proteins, suggesting structure-dependent complexity in lamin A/C functions. These findings also highlight the necessity to distinguish and separate the effects brought by different mutated isoforms of lamin A/C. Moreover, the observation

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that releasing progerin from nuclear periphery did not completely recover cellular mechanosensitivity suggests that there might be additional pathogenic mechanisms for mutated lamin A with the farnesylated tail, besides its ability to disturb cell mechanics by permanently attaching to the lamina network.

2.1.3 Lamin A/C Effects on Vasculature System and Endothelial Cells

Although lamin A and lamin C are broadly present in many differentiated tissues, their expression levels were reported to scale with tissue elasticity that is largely determined by the surrounding ECM. In other words, stiffer tissue elicited more lamin A/C expression, while softer tissue had B-type lamins dominant [105]. Moreover, exclusive lamin C expression was observed in mouse central nervous system (cerebellum and cortex) except in capillary endothelial cells and the meninges. This is proposed to be linked to miR-9, a brain specific microRNA that was bound to prelamin A and downregulated its expression [105,119]. Therefore, it is critical to be aware of the distinct expression patterns and functions that lamin A/C might have in tissues possessing different stiffness. Arterial stiffness, on another hand, is associated with other factors, including endothelial signaling and VSMCs (vascular smooth muscle cells) tone that were also found to be modified by lamin A/C [120-122]. Given the associated mechanical defects due to the genetically mutated lamin A, it is worthwhile to analyze how lamin A/C modifies vascular cells in cell mechanics.

Many articles have addressed the vascular specific disorders brought by abnormal lamin A/C. LMNA knockout mice that exhibited dilated cardiomyopathy (DCM) had altered nuclear shape and disrupted connections between the nucleus and desmin (muscle-specific IF) in cardiomyocytes and skeletal muscle cells [123-125]. Several missense mutations identified in patients with DCM were also found to affect cardiac conduction system or heart muscle [126]. Reduced lamin A/C expression that was induced by hypertension promoted the hyperproliferation of VSMCs, indicating the ability of lamin A/C in preventing stretch-induced VSMC proliferation. The suppressions of lamin A/C and nesprin expressions by low shear stress in primary rat aortic ECs also indicate the potential dysregulations of lamin A/C-related nucleo-cytoskeletal connections induced by abnormal mechanical stress in ECs [127]. These data suggest the mechanosensitive role of lamin A in vascular system. Further studies are needed to

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better understand the role of abnormal nuclear lamina in morphological remodeling processes of endothelial cells under flow.

2.2 Signaling Roles of A-type Lamins

Besides acting as a structural support to prevent the nucleus from breakdown, lamin A/C also binds to various transcription factors and chromatins. They are present both at the nuclear periphery and throughout the nucleoplasm to form relatively stable structures in a dynamic equilibrium state, and interact with other nuclear molecules to mediate cell functions [128].

2.2.1 Molecular Interactions of Lamin A/C

A-type lamins associate with chromatins at lamina-associated domains (LADs) that repress gene expression in most cases, and they also interact with many transcription factors to regulate cell differentiation and proliferation [129-134]. Qi, et al. classified the primary functions of DNA segments that were bound to lamin A/C in VSMCs, and more than 35% of the DNA was of the phosphoprotein category [135], indicating the role of lamin A/C in post-translational modifications and signaling molecules regulations. Abnormal fragmentation of heterochromatin, changes in epigenetic marks and mislocalizations of transcription factors were also reported in cells with deficient or mutated LMNA gene, suggesting their critical roles in maintaining cell functionality through epigenetic regulations [136-139].

Multiple mechanisms are believed to contribute to these lamin A/C-associated gene regulations such as: providing the interaction platform for signaling molecules, hampering the import of transcription factor units to inhibit signal transduction, as well as regulating tissue-specific pathways by organizing periphery heterochromatin [140]. For example, megakaryoblastic leukaemia 1(MKL1), a transcription factor that regulates cell differentiation, migration and proliferation, failed to localize to nucleus in LMNA$^{-/-}$ and LMNA N195K mutant MEFs due to defective actin dynamics and loss of emerin expression [141]. Impaired Wnt signaling and reduced nuclear localization of lymphoid enhancer binding factor (LEF1) in a HGPS mouse model were observed to affect ECM synthesis [142]. Moreover, the critical position of lamin A/C in nucleo-cytoskeletal coupling complex also facilitates their involvement in mechanotransduction pathways, for instance, the attenuated activation of NF-κB signaling by biaxial

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cyclic strain in LMNA$^{-/-}$ MEFs [143,144]. This finding suggests that mutation in or lack of lamin A/C can prompt not only changes in mechanical properties, but also in mechanotransduction pathways induced by external stimuli.

2.2.2 Lamin A/C in Mechanosignaling Pathways Associated with Atherosclerosis

Lamin A/C has been shown to participate in many mechanotransduction pathways in vascular cells, and their mutations can led to vascular dysfunctions in DNA repair and inflammatory responses [145,146]. Studies have revealed their pivotal roles in many mechanosignaling pathways to maintain vascular homeostasis, and changes in applied mechanical forces can interfere with lamin A/C-associated regulations in vascular cells. For instance, A-type lamins and emerin were reported to suppress VSMC proliferation *in vitro* under normal cyclic strain (5%), which was correlated with their associations with sequence-specific regions that enrich transcriptional factor motifs E2F1, E2F3, SP1 and Stat 1 [135]. Bovine aorta endothelial cells (BAEC) had defective shear stress-induced transcriptional activation of glucocorticoid response element (GRE) after silencing lamin A/C [147]. Low shear stress applied on primary aortic ECs resulted in increased proliferation and apoptosis in ECs, and the changes were shown to be induced by reduced lamin A/C expression and repressed activation of several TFs (Stat-1, Stat-3, Stat-5 and Stat-6) [127]. Those findings indicate the atheroprotective roles of lamin A/C in suppressing the stretch-induced VSMCs proliferation that can promote atherosclerotic lesion formation, as well as in participating shear stress-induced atheroprotective gene regulations in vascular ECs [11,148]. Moreover, the differential effects of lamin A expression on ECs and VSMCs in terms of low shear stress-induced secretary molecules PDGF-BB and TGF-β productions also indicate the existence of cell type-specific response of A-type lamins in vascular system [149].

There are mainly two types of laminopathies involving atherosclerosis progression, FPLD2 and HGPS. Patients with FPLD2 that carry LMNA mutation at 482 codon often developed coronary heart disease in their adulthood, especially in women [150,151]. It was believed that metabolic disorders like insulin resistance contribute most to the premature atherosclerosis [152,153], but a recent study revealed that the R482W LMNA mutation responsible for FPLD2 led to the cascade of endothelial dysfunctional

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events, including reduced NOS expression, activated proinflammatory molecules such as IL-6 and IL-8, and increased adhesion affinity with immune cells [154]. Similarly, the proinflammatory responses were also reported to be effected in HGPS ECs [7]. Combined with previous discussions of how hemodynamic forces regulate those endothelial functions in pathogenesis of atherosclerosis, it is suggested that the mutated lamin A/C isoforms can potentially disturb the atheroprotective pathways, and promote the expressions of atheroprone genes in endothelial cells at arterial sites that are exposed to irregular mechanical stresses.

3. Correlations Between Lamin A/C and Cellular Aging

Lamin A/C expression seems to be regulated throughout development. For instance, evidence showed that lamin A/C did not appear until embryonic cell differentiation and the downregulation of several pluripotency genes like Tra-1-60 and SSEA-4 [155]. Their expression levels also varied in differentiated human tissues with differences in tissue stiffness [105,156]. Changes of lamin A/C over time can lead to many epigenetic changes, such as the induction of aberrant pathways that promote tumor cell migration and invasion in several types of cancers as well as in the aging process, which will be addressed in the following section [157].

3.1 Lamin A/C in Aging Process and Progeriod Syndromes

Aging refers to the natural process that an organism undergoes over time, which comes with declinations in body functions and increasing probability of developing diseases and death. Many mechanisms of aging have been proposed recently, including genomic instability, telomere attrition, epigenetic alternations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction,cellular senescence, stem cell exhaustion, and altered intercellular communication [86,158]. Cell senescence is a state of arrested cells growth with altered gene expression profile. It is triggered either by telomere shortening (replicative senescence) or other damage signals before cells reach their limited lifespan (premature senescence) [159,160]. Recent studies in the structural and functional alternations of lamin A/C in aging-related diseases revealed the similarities between the underlying mechanisms of laminopathies with that of aging pathologies, especially in nuclear architecture changes,

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chromatin and epigenetic modifications and activation of senescence pathways [161-163]. Some aging phenotypes such as cellular senescence and telomere dysfunction were induced by several laminopathies or diseases with abnormal Zmpste24 expression [164-167]. These abnormalities have motivated the research on how lamin A/C-related dysfunctions contribute to the normal aging process.

Many studies have addressed the role of progerin, the aberrant prelamin A isoform that causes HGPS, in contributing to accelerated aging. The expression of exogeneous progerin in normal fibroblast can induce replicative senescence and loss of telomeres, suggesting conserved progerin-dependent senescence pathways in normal cells [166]. In HGPS fibroblasts, progerin also accumulated in culture, accompanied with deteriorated nuclear shape and disorganized methylation pattern of histone 3 on lysine 9 (H3K9) that overlapped with the phenotypes found in aged cells [168]. Positive detection of Δ150 LMNA mRNA that was responsible for progerin synthesis was reported in normal fibroblasts, and the use of cryptic splicing site increased as the passage went up regardless of donors' age [169]. Meanwhile, the localization of wild type lamin A/C was also altered in cells from old donors, where they were more accumulated at the nuclear envelope instead of present at both nuclear periphery and nucleoplasm as in young donor cells. Removal of progerin in cells from old individuals by the inhibition of the cryptic splicing site has rescued the nuclear defects in terms of the expression patterns of nuclear protein (HP1) and histone modifications (Tri-Me-K9H3) [170]. It is not yet known how progerin takes effects in normal aged cells at a very low expression level that did not change significantly over age (although the increasing trend was observed over *in vitro* culture) [171]. On the other hand, the downregulation of Zmpste24 gene due to increased sensitivity to oxidative stress during aging might be another cause for the prelamin A accumulation in aged cells [172]. Lack of Zmpste24 will interfere the prelamin A posttranslational modifications, and lamin A isoforms that possess the permanently farnesylated tail will be generated instead of the mature form [173,174].

3.2 Molecular Mechanisms of Lamin A/C-dependent Premature Aging

Multiple but not mutually exclusive mechanisms were proposed about how lamin A/C participates in cell senescence. Some studies hypothesized that progerin production in HGPS cells was

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mediated by SRSF1 (serine-arginine rich splicing factor 1) and SRSF6, whose expressions were also age-dependent [175,176]. Gene therapy to block the aberrant splicing site reversed the nuclear defects, and treated HGPS mice had elongated life span [177]. Another treatment by FTIs that inhibit prelaimin A farnesylation had rescued nuclear shape, and improved bone structure and vascular stiffness in both mouse models and patients with HGPS, as well as prevented SMC loss in mice model [178-183]. However, this treatment did not ameliorate DNA damage or reactivate checkpoint signaling pathways in HGPS and RD human fibroblasts. Other remnant problems of this treatment like the universal effects of FTI on farnesylation inhibition, and the retention of prelamin A at nucleoplasm still remain to be solved [184].

Another hypothesis is that, the prelamin A-associated cell aging is caused by telomere shortening that can lead to alternative splicing events in multiple genes including LMNA [171]. Aberrations in chromosomes and telomeres were observed after inducing progerin into normal human dermal fibroblasts [167]. The introduction of exogenous telomerase into HGPS fibroblasts can significantly enhance cell propagation ability and prevent senescence with unchanged progerin level over passages, probably by interacting with telomeres and repressing p53 and Rb tumor-repressor pathways [171]. The production of progerin was only seen in cells with short telomeres, but was not observed in telomore-independent premature senescence induced by sodium butyrate or a histone deacetylase inhibitor [171]. These findings suggest that progerin-induced senescence was specifically driven by telomere shortening. However, this hypothesis remains to be challenged as limited signals were tested in this study.

Besides telomere shortening, the extensive damage in DNA repair system and the changes in lamin A-associated regulating pathways were also reported to be potential mechanisms of cellular aging. Increased DNA damage, as well as the failure to respond to DNA damage and the hyperactivation of p53 tumor suppressor pathway, were observed in Zmpste24 $^{-/-}$ fibroblast, indicating dysregulated DNA repair in response to accumulated farnesylated prelamin A [163,185]. As a result of DNA damage in Zmpste24 deficient mice, NF-κB inflammatory signaling pathway was activated by a protein kinase ATM (staxia-telangiectasia mutated) and its downstream factor NF-κB essential modulator (NEMO). This pathway was

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involved in some progeroid phenotypes in those mice, since blocking the pathway greatly improved their biological characteristics [186-188]. However, the intact DNA repair pathways observed in a progeria mouse model with lamin A exon 9 deleted may indicate the trivial role of exon 9 region in maintaining genome stability [189]. Changes in epigenetic marks such as H3K27me3 and their causative heterochromatin reorganizations in human HGPS fibroblasts occurred prior to aberrations in nuclear shape [190]. Together with changes in histone methylation in HGPS and aging cells, these data suggest that general mechanisms of epigenetic control were shared by normal aging process and prelamin A-induced premature aging diseases[91]. A more recent study showed that signaling pathway driven by a sequestered transcription factor NRF2 (nuclear factor (erythroid-derived)-like 2) was impaired in HGPS fibroblasts. It is a substrate for CAND1 gene with the capacity to prevent HGPS defects *in vitro*. NRF2 expression was closely associated with progerin expression, antioxidant gene activation, and cell survival [191]. Although reactivation of NRF2 pathway did not completely restore all progerin-induced defects, this finding disclosed one of the molecular mechanisms in progerin-induced cellular defects, and provided new insight into lamin-A associated aging process.

Furthermore, recent advances in stem cell research also indicate that regenerative dysfunctions may also contribute to premature aging [192,193]. The multiple roles that Notch signaling plays in vascular system may also be the link between progerin and vascular dysregulations. Notch signaling pathway was activated by ectopic progerin expression in human mesenchymal stem cells (hMSCs) [194]. The capacity of hMSCs to differentiate into adipocytes was largely compromised, which is consistent with the subcutaneous adipose tissue loss in HGPS patients [195].

Overall, efforts have been invested to explore the underlying mechanisms of prelamin A induced-senescence. Confirmations of the role of prelamin A in *in vivo* aging and comparison of molecular mechanisms in normal and premature aging laminopathies are needed to further understand how immature lamin A contributes to the aging process.

3.3 Lamin A/C in Vascular Aging

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As healthy individuals age, the risk of developing cardiovascular disease increases with age as a result of changes in in structure and functions of the vasculature [196-198]. Age-associated changes in vascular cells and ECM composition, such as elevated secretion of proinflammatory factors, increased invasive and migratory potentials, reduced production of vasodilators, as well as the changes in collagen and elastin components can lead to altered mechanical properties of vessel wall and inflammation [199,200]. For example, the stiffness and adhesion capacity of VSMCs were increased with aging [201], and the expression pattern of Sirt1, a deacetylase involving in multiple cellular events including anti-inflammatory pathways in endothelial cells [202], was observed to be repressed in vascular aging [203]. Similar phenotypes were reported in prelamin A-induced progeroid syndromes, including characteristics of stiffened and calcified vessel wall, and activation of ICAM-1 and monocytes adhesion in ECs [204-206]. Nevertheless, different phenotypes also existed between HGPS and aging individuals that were summarized by Brassard and colleagues [199], such as extensive atherosclerotic lesions, increased platelet count, prolonged prothrombin times, as well as the preserved flow-mediated dilation response in HGPS vessels, indicating dose-dependent effects of progerin in vascular system [207]. However, considering the similar vascular defects induced by prelamin A and physiological aging, the prelamin A-associated changes in vasculature may still be indicative of vascular aging.

Evidence of restrictive detection of progerin in vascular cells from a HGPS patient indicates the preference of progerin accumulation in vascular system [100], and the activations of inflammatory responses and cell senescence in vascular ECs from FPLD2 patients also suggest the onset of atherosclerosis [154]. Immunostaining in a progeria mouse model revealed a significant loss of SMCs in large arteries accompanied with replacement of proteoglycan (PG) and collagen, and it was followed by adventitial thickening and arterial wall calcification that were the main contributors to vascular stiffening [204,208]. Several progeria mouse models were created to study the mechanisms underlying prelamin A-induced premature aging, but not all HGPS syndromes were recapitulated by these models [90], for instance, the observation of intimal thickening in HGPS patients was not reported in the mouse model

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[208], indicating the differences in progeria models across species, and the necessity of confirming the pathological findings in humans.

Similarly, prelamin A accumulation in normal aging vascular cells can also impair their functions and disturb the vascular remodeling process. The detection of endogenous prelamin A was reported in VSMCs either from aged individuals or by serial culture *in vitro*, and it was accompanied with the increased sensitivity towards differentiation prior to compromised proliferation capacity, suggesting that prelamin A accumulation precedes the onset of senescence [55]. Although this attenuation was believed to be initiated by the downregulation of Zmpste24 along with cellular senescence [209], their expressions were heterogeneous in advanced atherosclerotic lesions, indicating additional regulatory factors responsible for prelamin A accumulation [55]. ECs and endothelial progenitor cells with inhibited Zmpste24 activity overexpressed farnesylated prelamin A, and the inflammatory factor ICAM-1 was activated (but not VCAM-1 and E-selectin), and the adhesion of monocyte was enhanced in ECs. The regenerative capacity in endothelial progenitor cells was also impaired in terms of microvascular network generation, which indicates the exhaustion of endothelial stem cell pool [206], together with the observation of reduced migration potential in melanoma cells overexpressing Δ50 lamin A explain the low incident rate of cancer in progeria patients, since neovascularization is critical for cancer development and progression [210,211].

Besides the potential mechanisms discussed in the last section, altered cellular responses toward mechanical stresses were also closely linked to prelamin A-associated vascular disorders [199]. Cytoskeletal reorganizations, such as the reduced expressions of cytoskeletal proteins in SMCs under high shear stress in a progeria mouse model, were potentially responsible for the SMC loss in the medial layer of aorta during vasculopathy development [212]. Alternations in the mechanical properties of the vessel wall by prelamin A, such as vascular stiffening, were also critical in promoting vascular diseases [213]. One of the causes - ECM composition changes and the resulting proliferation arrest were observed in lamin A mutated fibroblasts, which is led by impaired Wnt signaling [142].

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Overall, abnormalities in lamin A/C have been suggested to cause premature aging phenotypes and influence vascular system functions. The observations of prelamin A accumulation in normal aged cells also indicate the pivotal roles it could play in promoting the aging process and vascular diseases. Further validations of how prelamin A participates in cellular senescence and vascular aging, as well as their associated pathways are needed to assist in developing therapeutic mechanisms for prelamin A-induced premature aging diseases.

4. Conclusion

Previous studies have demonstrated that, the development of atherosclerosis was closely related to the hemodynamic forces that stimulate various responses in vascular cells. On the other hand, the abnormalities of LMNA gene expression were reported in either healthy aged cells or cells from patients with lamin A-associated aging syndromes. Considering the mechanosensitive roles that lamin A plays in vascular cells, it is important to investigate whether lamin A can mediate these stress-induced responses, which could be an underlying mechanism that contributes to the initiation of cardiovascular diseases.

Besides the advances in research that were discussed above, there are several remaining concerns to be addressed to fully understand the relationship between A-type lamins and atherosclerosis development during aging. For example, what are the functional differences between lamin A and lamin C in the mammalian cell aging process, and are they complementary to each other? How do senescent cells communicate with its surrounding non-senescent cells to achieve tissue-level changes? Ongoing research on these topics will help to explain the occurrence of laminopathies with accelerated aging syndrome, as well as the onset of vascular diseases with aging as the risk factor.

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Acknowledgement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare that there are no conflicts of interest. A signed Conflict of Interests Policy Form is submitted.

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