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Lamin in inflammation and aging

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Aging is characterized by a progressive loss of tissue function and an increased susceptibility to injury and disease. Many age-associated pathologies manifest an inflammatory component, and this has led to the speculation that aging is at least in part caused by some form of inflammation. However, whether or not inflammation is truly a cause of aging, or is a consequence of the aging process is unknown. Recent work using *Drosophila* has uncovered a mechanism where the progressive loss of lamin-B in the fat body upon aging triggers systemic inflammation. This inflammatory response perturbs the local immune response of the neighboring gut tissue and leads to hyperplasia. Here, we will discuss the literature connecting lamins to aging and inflammation.

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Introduction

Chronic systemic inflammation without apparent infection in elderly humans is often referred to as the 'inflammaging' phenotype, and is primarily characterized by elevated levels of circulating pro-inflammatory cytokines [1–6]. Epidemiological studies have found a strong correlation between the inflammaging phenotype and the presence of several aging-associated pathologies [7–9]. Genome-wide association studies have implicated several genes that function in immune, inflammatory and stress responses as being modifiers of longevity and health span [10].

Understanding the contribution of inflammation to aging has been pursued for many years with much effort aimed at identifying biomarkers of aging and cellular events that might serve as triggers for inflammatory responses. While conceptually straightforward, identifying cellular events has been very difficult, and is still largely correlative. Further, understanding the consequences of inflammation on aging presents its own challenges because, in part, many age-related diseases such as cardiovascular disease and osteoarthritis invoke strong inflammatory responses [11].

Recent studies have implicated the involvement of the nuclear intermediate filament proteins, the lamins, in aging-related inflammation. Here we will first introduce the general functions of lamins and then discuss the studies connecting these proteins to inflammation and aging.

Nuclear lamins

Nuclear lamins are classed as type V intermediate filaments. There are two lamin subtypes, A-type and B-type, which are distinguished by their protein sequences, physical properties and expression profiles. In humans, the A-type lamin is encoded by *LMNA*, while two separate genes, *LMNB1* and *LMNB2*, encode the B-type lamins. In *Drosophila*, the subject of some discussion below, the A-type and B-type lamins (LAMC and LAM) are encoded by *LamC* and *Lam*, respectively.

Alternative splicing of the human *LMNA* transcript produces the major lamin-A and lamin-C isoforms. Lamin-C lacks the final two exons found in lamin-A, and is not post-translationally processed like either lamin-A or the B-type lamins. Post-translational processing of this latter group involves a carboxyl-terminal farnesylation motif (CaaX). The cysteine residue of this motif is first farnesylated. A proteolytic event removes the 'aaX' and then the farnesylcysteine is methylated. For B-type lamins, there is no further processing and the farnesylation is a permanent feature of the protein. In the case of lamin-A, however, the carboxyl-terminus undergoes a second proteolytic cleavage to produce a mature unfarnesylated protein [12]. A zinc metalloprotease known as Zmpste24 performs both proteolytic processing steps required for production of mature unfarnesylated lamin-A while the 'aaX' in B-type lamin is removed by a protease known as Rce1 [13–15].

The lamins are believed to assemble into a dense meshwork underneath the inner nuclear envelope. This meshwork can serve as an interaction node for chromatin and proteins of the nuclear periphery [16,17•]. Considering the diversity of these interactions, it is not surprising that

lamins function in different nuclear activities such as chromatin organization, DNA replication, transcriptional regulation, signal transduction, and nuclear shape maintenance [12,18–20]. Consequently, lamins are viewed as housekeeping proteins that are essential for cell viability.

More recent studies, however, have shown that mouse embryonic stem cells (mESCs) completely lacking lamin proteins can self-renew and differentiate *in vitro* [21••]. Thus, lamins are not required for the survival of at least this cell type. The study of lamins in different model organisms suggests that lamins are required for the proper development of several organs (e.g., brain, the diaphragm, and the testis) [22•,23–25]. This idea is also supported by the discovery of tissue-specific diseases caused by mutations in lamin genes. For example, different mutations in *LMNA* cause a spectrum of disorders ranging from dilated cardiomyopathy, to partial lipodystrophy, and to the segmental premature aging syndrome, Progeria [26–28]. To date, there are no reported mutations in *LMNB1* that cause disease; however, duplication of this gene causes an adult-onset form of leukodystrophy [29]. *LMNB2* has also recently been linked to a progressive form of epilepsy [30]. How lamins cause tissue-specific diseases remains unclear.

Lamin-A: aging and inflammation

Hutchinson-Gilford Progeria Syndrome (HGPS) is an exceptionally rare disorder that resembles premature aging. Most HGPS patients harbor the same *LMNA* mutation, a *de novo* C1824T change that enhances the use of a cryptic splice site and leads to the production of a permanently farnesylated form of lamin-A [31•,32•]. This aberrant form of lamin-A, termed progerin, causes nuclear blebbing, down-regulation of some nuclear envelope proteins, accumulation of DNA damage and accelerated cellular senescence [31•,33,34]. Surprisingly, progerin mRNA has been detected at low level in both young and aged individuals, and some, but not all studies on the subject indicate that the progerin product appears more abundantly in select tissues from aged individuals [35•,36–38]. While it is uncertain if there is any function for the progerin present in these tissues, progerin can be induced upon UV damage and might represent an extension of the DNA damage response [39••].

Markers of inflammation have been examined in HGPS patient samples and mouse models for this disorder. Cells derived from HGPS patients show an elevated NF-κβ transcriptional response profile [40]. The overexpression of an atypical-HGPS *LMNA* mutant also increases mRNA levels of certain inflammatory cytokines [41]. Further, inflammatory markers are elevated in the arteries, liver and skin of Progeria mouse models (both *Lmna* and *Zmpste24*) [38,42••,43,44]. While the basis of this is not well understood, inflammation appears to be a part of the accelerated aging phenotype caused by *LMNA* mutations.

Lamin B: aging and inflammation

Human and mouse primary cell lines have a finite replicative lifespan (Hayflick limit) when cultured *in vitro*. This phenomenon, more commonly called replicative senescence, is characterized by cessation of cell division, increased secretion of inflammatory factors and changes in cell morphology and chromatin organization [45,46]. Recent studies have found that the replicative senescence of cultured mammalian fibroblasts is accompanied by lamin-B1 reduction [47••,48••,49]. The induction of senescence in cell culture by expression of oncogenic Ras, or activation of the downstream Rb or p53 tumor suppressors also leads to lamin-B1 decline [47••,48••]. Additionally, lamin-B1 reduction was detected in senescence-prone fibroblasts derived from Progeria patients and in cells with shortened telomeres or other forms of DNA damage [34,48••,49,50••,51]. *In vivo*, the irradiation of mice leads to cell senescence and lamin-B1 loss in the liver [48••]. The loss of lamin-B1 appears to be regulated at both mRNA and protein levels [48••,49,52••,53••]. There are, however, studies that show the association of increased lamin-B1 protein level and senescence [49,54••]. In these studies, the overexpression of lamin-B1 in primary fibroblasts was sufficient to drive cells towards senescence whereas depletion resulted in proliferative arrest [49,54••]. While there is no clear rationale for why lamin-B1 levels change under any of these conditions, lamin-B1, whether it is a reduction or increase in protein level, appears to be a marker of cellular senescence and various forms of cellular stress [48••,54••].

The human skin is the only organ reported to naturally have an age-related loss of lamin-B1 [49]. In an effort to explore this potential relationship in other tissues, we analyzed lamin levels in different organs from young and old *Drosophila* [55••]. *Drosophila* is a tractable model for studies of aging, inflammation and lamins as this model is relatively short-lived and is historically important in the immunity field [56,57]. Further, the *Drosophila* system is armed with an extensive set of genetic tools and methods that facilitate tissue-specific *in vivo* experimentation [56]. We found that B-type lamin (LAM), but not A-type lamin (LAMC), was reduced in the brain (Figure 1a,b, unpublished observations) and the fat body (Figure 1c) [55••]. Notably, not all tissues (e.g., gut, heart) lose LAM upon aging (Figure 1c). One possibility is that gut epithelium was continuously replaced by intestinal stem cells and so senescent cells were simply replaced. However, in post mitotic heart cells and oenocytes, which persist throughout the life of the fly, lamin loss was not apparent [55••]. The simplest interpretation from these observations is that age-related loss of B-type lamin occurs in select tissues. What makes these tissues susceptible to lamin-B loss is unknown.

While there is some evidence that links B-type lamin and inflammation, this aspect has not been thoroughly