

Protein sequestration at the nuclear periphery as a potential regulatory mechanism in premature aging

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Despite the extensive description of numerous molecular changes associated with aging, insights into the driver mechanisms of this fundamental biological process are limited. Based on observations in the premature aging syndrome Hutchinson–Gilford progeria, we explore the possibility that protein regulation at the inner nuclear membrane and the nuclear lamina contributes to the aging process. In support, sequestration of nucleoplasmic proteins to the periphery impacts cell stemness, the response to cytotoxicity, proliferation, changes in chromatin state, and telomere stability. These observations point to the nuclear periphery as a central regulator of the aging phenotype.

Introduction

Physiological aging is generally defined as a decline in function over time from the cellular to organismal level (López-Otín et al., 2013). As a consequence, with increasing age we are faced with an elevated risk for a spectrum of complex diseases (see text box Premature aging disorders and the nucleus; Chung et al., 2009; Campisi, 2013; Kubben and Misteli, 2017). Deterioration of cellular functions occurs in response to both cell-intrinsic alterations, such as mitochondrial dysfunction and differentiation capacity, and environmental influences, including nutrient availability and endocrine signaling (López-Otín et al., 2013). Although the molecular details that regulate the aging process have remained largely elusive, several characteristics of aging are pervasive. These include changes in nutrient sensing, intercellular communication, proteostasis, mitochondrial dysfunction, cellular senescence, and adult stem cell exhaustion as well as nucleus-specific changes, including altered epigenetic marks, increased genome instability, and telomere attrition (López-Otín et al., 2013). The relative contributions and interdependence of these pathways to the aging process remain largely unclear.

Epidemiological studies have provided key details regarding the risk factors for human longevity (Sebastiani et

al., 2012; López-Otín et al., 2013). Nevertheless, given ethical and practical issues in the study of human aging, model systems with shorter lifespans, such as yeast, worms, flies, fish, and mice, have been used extensively to gain molecular insight into evolutionarily conserved mechanisms of longevity and aging (Mitchell et al., 2015). These models have substantiated that aging involves defined cellular pathways that can be experimentally manipulated. A limitation of using animal models, especially non-mammalian systems, to deduce mechanisms of human aging is that the extent they recapitulate the human pathology is highly variable and largely unknown. For example, many short-lived animals used for aging studies such as *Caenorhabditis elegans*, zebrafish, killifish, mice, and rats, typically die of old age with intact and relatively long telomeres, whereas in aged humans, telomeres are shortened (Blackburn et al., 2015). In addition to their more complex physiology, humans, in contrast to laboratory animals, are exposed to complex environmental influences which in all likelihood contribute to aging. To circumvent some of these limitations, the existence of a wide set of genetic disorders that cause accelerated aging in humans has been exploited (see text box).

Premature aging disorders, or progerias, allow a unique glimpse into the potential mechanisms underlying physiological aging. However, given that no premature aging disorder fully recapitulates all features of human aging, these disorders are designated as segmental progerias (Dreesen and Stewart, 2011; Kubben and Misteli, 2017). Nevertheless, premature and physiological aging share similar features, and the insights gained from premature aging models appear often applicable to physiological aging (Dreesen and Stewart, 2011; López-Otín et al., 2013; Kubben and Misteli, 2017). Conversely, understanding the discrepancies between premature and physiological aging has also proven to be illuminating, such as in highlighting the molecular relationships between oncogenesis and aging (Fernandez et al., 2014; Zane et al., 2014). Intriguingly, a disproportionate number of premature aging disorders have been mapped to defects in nuclear proteins. In this Perspective, we discuss the contribution of nuclear dysfunction to pathological aging, and we specifically posit that the inner nuclear membrane (INM) and the lamina are regulators of the aging phenotype.

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Abbreviations used: AKTIP, AKT-interacting protein; HGPS, Hutchinson–Gilford progeria syndrome; hTERT, human telomerase reverse transcription; INM, inner nuclear membrane; LEF, lymphoid enhancer binding factor; MSC, mesenchymal stem cell; PCNA, proliferating cell nuclear antigen; Rb, retinoblastoma protein; ROS, reactive oxygen species; S1P, sphingosine-1-phosphate; TRF, telomere repeat-binding factor.

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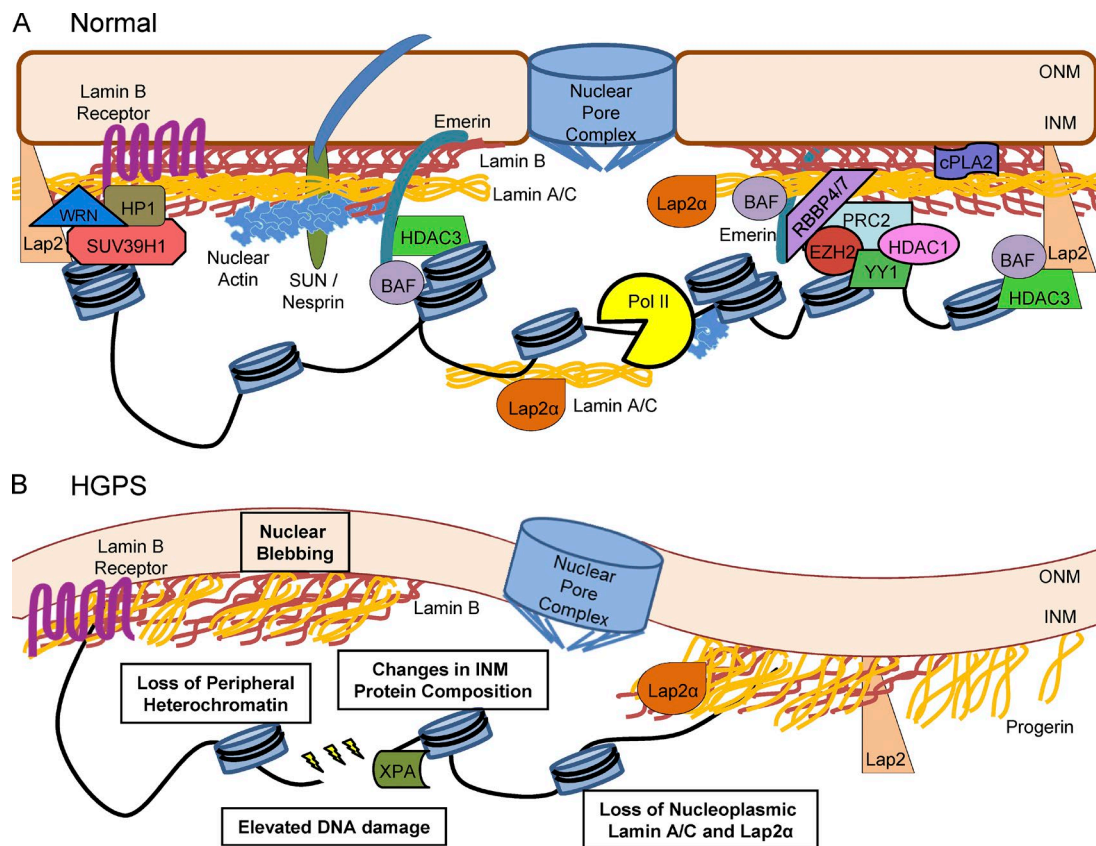


Figure 1. The INM and lamina in normal and HGPS nuclei. (A) The INM is composed of an array of proteins responsible for maintaining nuclear function and an associated protein meshwork composed of tetrameric lamin filaments (Turgay et al., 2017). The nuclear lamina is composed of B-type lamins that are integrated into the INM and proximal but segregated lamin A/C filaments (Delbarre et al., 2006; Shimi et al., 2008, 2015; Xie et al., 2016). The structural integrity of the nucleus is also influenced by the SUN/Nesprin LINC complex that links the nucleus to the cytoskeleton (Zhang et al., 2005; Chang et al., 2015). Furthermore, integral INM proteins such as lamin B receptor, emerin, and Lap2 isoforms maintain heterochromatin at the periphery by interacting with chromatin remodeling complexes WRN, HP1/SUV39H1, PRC2/NURD, and HDAC3/BAF (Makatsori et al., 2004; Somech et al., 2005; Shumaker et al., 2006; Holaska and Wilson, 2007; Montes de Oca et al., 2009; Pegoraro et al., 2009; Demmerle et al., 2012; Laugesen and Helin, 2014; Cesarini et al., 2015; Zhang et al., 2015b). Additionally, peripheral and nucleoplasmic lamin A/C may have different roles in transcription and replication via regulation of Lap2α, nuclear actin, and polymerases (Pol II; Dechat et al., 2000; Nili et al., 2001; Pekovic et al., 2007; Simon et al., 2010; de Lanerolle and Serebryanny, 2011; Vidak et al., 2015). Through these interactions, the INM maintains proper DNA replication, DNA repair, proliferation, proinflammatory signaling via cytosolic phospholipase A2 (cPLA2), and differentiation (Dittmer and Misteli, 2011; Burke and Stewart, 2013; Enyedi et al., 2016). (B) Progerin expression and incorporation into the INM disrupts nuclear organization, causing misshapen nuclei (Goldman et al., 2004; Dahl et al., 2006; Verstraeten et al., 2008). HGPS models exhibit reduced expression of integral INM proteins such as lamin B1 and isoforms of Lap2 (Scaffidi and Misteli, 2005) and a corresponding loss of peripheral heterochromatin (Goldman et al., 2004; Scaffidi and Misteli, 2005; Shumaker et al., 2006; McCord et al., 2013). Not only is the composition of the periphery altered, but nucleoplasmic protein populations are also lost (i.e., lamin A/C and Lap2α; Dechat et al., 2000; Chojnowski et al., 2015; Vidak et al., 2015). These defects correlate with increased DNA damage, abnormal DNA damage repair, and impaired proliferation (Decker et al., 2009; Benson et al., 2010; Cao et al., 2011a; Musich and Zou, 2011; Chojnowski et al., 2015).

The INM

The distinguishing feature of eukaryotes is the nucleus: a segregated organelle that houses the genetic information of the cell. The nucleus is composed of a membrane bilayer: the outer nuclear membrane is contiguous with the ER and links the cytoskeleton to the nucleus, and the INM maintains nuclear architecture and aids in proper function (Hetzer, 2010; Fig. 1). The two nuclear membranes are connected at the numerous nuclear pore complexes that selectively traffic proteins between the cytoplasm and the nucleus (Katta et al., 2014).

The INM contains a number of integral scaffolding proteins (e.g., emerin, LBR, Lap2β, SUN, and MAN1; Schirmer and Gerace, 2005) and is supported by an associated 3.5-nm protein meshwork composed of tetrameric lamin filaments, referred to as the nuclear lamina (Turgay et al., 2017; Fig. 1 A). In mammals, there are three differentially expressed lamin genes: *LMNA*, *LMNB1*, and *LMNB2* (Dittmer and Misteli, 2011).

LMNA is alternatively spliced into two major isoforms, lamin A and C. B-type lamins are incorporated into the INM, whereas an associated lamin A network is thought to remain proximal but largely segregated (Delbarre et al., 2006; Goldberg et al., 2008; Shimi et al., 2008, 2015; Xie et al., 2016). In addition to the lamina, the INM is physically connected to the cytoskeleton via the linker of nucleoskeleton and cytoskeleton complex (LINC; Lombardi and Lammerding, 2011; Chang et al., 2015). In this way, the nuclear periphery integrates both signaling and mechanical cues to regulate gene expression and gene positioning, as well as DNA replication, DNA repair, proliferation, proinflammatory signaling, and differentiation (Dittmer and Misteli, 2011; Burke and Stewart, 2013; Enyedi et al., 2016).

Proteomic analyses have highlighted the complexity of the INM. Earlier studies found that the INM is composed of ~70 proteins involved in protein scaffolding, maintenance of structural stability, and genomic regulation (Dreger et al., 2001;

Schirmer et al., 2003; Schirmer and Gerace, 2005). More recent research describes several hundred to several thousand proteins enriched at the nuclear envelope in a tissue-specific manner (Korfali et al., 2010, 2012; Wilkie et al., 2011; Smoyer et al., 2016; Thul et al., 2017). These discrepancies may be explained by a model wherein ER proteins that pass through the nuclear pore complex can diffuse along the INM, but only a subpopulation is retained (Ungricht et al., 2015; Smoyer et al., 2016). Evidence relating INM composition with function has come from INM-associated protein mutations that map to numerous pathologies including Charcot-Marie-Tooth disease, limb-girdle and Emery–Dreifuss muscular dystrophies, several myopathies, and most strikingly, premature aging disorders (Schirmer et al., 2003; Somech et al., 2005; Dittmer and Misteli, 2011).

Premature aging and the nuclear periphery

Strong evidence for a role for regulatory events at the nuclear periphery in aging comes from the premature aging disorder Hutchinson–Gilford progeria syndrome (HGPS; Fig. 1 B). This rare childhood disease, which occurs at a rate of ~1 in 4 million births, is caused by a silent single-base mutation (classically 1824C > T) in the *LMNA* gene, and its symptoms include abnormal dentition, hair loss, joint contractures, growth retardation, lipodystrophy, osteoporosis and bone hypoplasia, sclerodermatous skin, skeletal muscle atrophy, and premature atherosclerosis with resultant cardiac failure in the early teens (De Sandre-Giovannoli et al., 2003; Eriksson et al., 2003; Merideth et al., 2008). The disease-causing mutation introduces a cryptic splice site in *LMNA* exon 11, resulting in heterozygous expression of a truncated form of lamin A, termed progerin (De Sandre-Giovannoli et al., 2003; Eriksson et al., 2003). Lamin A undergoes several processing steps including C-terminal farnesylation and subsequent cleavage by the endoprotease Zmpste24 (FACE-1), as well as tail methylation by isoprenylcysteine carboxylmethyltransferase (Barrowman and Michaelis, 2009; Davies et al., 2009; Ibrahim et al., 2013). Progerin, however, fails to undergo complete processing because it lacks the Zmpste24 cleavage site as a consequence of aberrant splicing in *LMNA* exon 11 caused by the disease mutation. Progerin incorporation into the nuclear lamina is thought to disrupt the lamin A and B networks, contributing to both structural and signaling dysfunction (Delbarre et al., 2006; Lee et al., 2016). In addition to classical HGPS, other mutations in lamin A can lead to atypical progerias that have symptoms similar to those of HGPS with varying severity (Chen et al., 2003; Csoka et al., 2004; Plasilova et al., 2004; Verstraeten et al., 2006; Liang et al., 2009; Doubaj et al., 2012). Mutations in *ZMPSTE24* have also been documented, resulting in the accumulation of a farnesylated lamin A (prolamin A) and leading to restrictive dermopathy (RD), a usually more severe form of HGPS (Moulson et al., 2005; Navarro et al., 2005, 2014; Wang et al., 2016).

At the cellular level, progerin-expressing cells exhibit misshapen and lobulated nuclei both in vitro and in vivo, with some cell types affected more than others (De Sandre-Giovannoli et al., 2003; Goldman et al., 2004; Navarro et al., 2004; Dahl et al., 2006; Verstraeten et al., 2008). HGPS-induced changes in the nuclear lamina correlate with reduced expression of lamin B1 and some isoforms of the chromatin-binding Lap2 proteins (Scaffidi and Misteli, 2005). Lamin B1 loss has been observed in multiple models of cellular senescence and has been linked to changes in chromatin organization (Dreesen et al., 2013; Shah et al., 2013; Zhang et al., 2016). Furthermore, HGPS cells show

a loss of peripheral heterochromatin (Goldman et al., 2004); repressive histone marks (H3K9me3 and H3K27me3; Scaffidi and Misteli, 2005; Shumaker et al., 2006; McCord et al., 2013; Zane et al., 2014); and association with heterochromatin protein 1 (HP1), enhancer of zeste homologue 2 (EZH2; Shumaker et al., 2006), and barrier to autointegration factor (BAF; Capanni et al., 2010; Loi et al., 2016). Intriguingly, BAF gene mutations result in Nestor–Guillermo progeria syndrome, a disease similar to, but less severe than, HGPS (Cabanillas et al., 2011; Puente et al., 2011). Along with changes in organization at the periphery, HGPS animal models also exhibit loss of the nucleoplasmic populations of lamin A/C and Lap2α (Naetar et al., 2017). These nucleoplasmic pools have been implicated in maintaining chromatin organization and gene expression and depletion of these nucleoplasmic pools may exacerbate the aging phenotype.

HGPS models exhibit defects in DNA replication, the cell cycle, and proliferation (Goldman et al., 2004; Dechat et al., 2007; Musich and Zou, 2011; Tang et al., 2012). These deficiencies correlate with increased DNA damage, abnormal DNA damage repair, and telomere dysfunction (Decker et al., 2009; Benson et al., 2010; Cao et al., 2011a; Musich and Zou, 2011; Chojnowski et al., 2015; Fig. 1 B). Progerin expression also leads to extranuclear defects such as inflammation (Di Micco et al., 2016; Tran et al., 2016), increased mitochondrial dysfunction (Peinado et al., 2011; Richards et al., 2011; Rivera-Torres et al., 2013; Kubben et al., 2016; Xiong et al., 2016), altered autophagy activation (Mariño et al., 2008), and changes to the ECM (Csoka et al., 2004; Hernandez et al., 2010; de la Rosa et al., 2013; Vidak and Foisner, 2016). Globally, proteomic and yeast two-hybrid screens have identified 35 and 225 proteins, respectively, that differentially interact with progerin versus wild-type lamin A (Kubben et al., 2010; Dittmer et al., 2014). Furthermore, RNA profiling has found drastic changes in the transcription program of HGPS models (Ly et al., 2000; Csoka et al., 2004; Scaffidi and Misteli, 2008; Marji et al., 2010; Kubben et al., 2012; Wang et al., 2015; Chen et al., 2017), which may be a consequence of the role of the lamina in gene positioning (Meaburn, 2016; Shachar and Misteli, 2017) and transcription regulation (Kumaran et al., 2002; Spann et al., 2002).

In normal human fibroblasts, progerin expression can be induced as a consequence of telomere shortening or uncapping (Cao et al., 2011a), as well as UV damage (Takeuchi and Rüdiger, 2013), strongly suggesting that aging may directly influence nuclear integrity. In support, several studies have reported increased sensitivity to or accumulation of progerin or prelamin A in physiological aging models (Cao et al., 2007; McClintock et al., 2007; Scaffidi and Misteli, 2008; Rodriguez et al., 2009; Marji et al., 2010; Olive et al., 2010; Ragnauth et al., 2010; Luo et al., 2013; Lattanzi et al., 2014; Petrini et al., 2017). Furthermore, single nucleotide polymorphisms in *LMNA* have been correlated with long-lived individuals (Conneely et al., 2012), and treatments that increase human longevity (i.e., rapamycin, metformin, statins) appear to alleviate symptoms of HGPS, at least in vitro (Varela et al., 2008; Cao et al., 2011b; Egesipe et al., 2016). Conversely, some HIV protease inhibitor treatments impair Zmpste24 function and lead to HGPS-like defects (Barrowman and Michaelis, 2009; Mehmood et al., 2016). Whereas the accumulation of progerin has a dose-dependent effect on cellular dysfunction (Moulson et al., 2007; Hisama et al., 2011; Chojnowski et al., 2015), the depletion of progerin by reversion of HGPS-derived fibroblasts into induced pluripotent stem cells reverses nuclear

Premature aging disorders and the nucleus

Most human premature aging disorders are caused by mutations in the cellular machinery involved in DNA metabolism (i.e., DNA replication, epigenetic regulation, telomere maintenance, and DNA damage signaling and repair). For example, mutations in *LMNA* cause HGPS and atypical Werner syndrome, mutation of *ZMPSTE24* causes restrictive dermopathy, and mutations in *BANF1* cause Nestor–Guillermo progeria syndrome (see Premature aging and the nuclear periphery). In addition, mutations in the RecQ helicases WRN, BLM, and RecQL4 cause the premature aging disorders Werner syndrome, Bloom syndrome, and Rothmund–Thomson syndrome, respectively. These helicases have conserved as well as nonredundant functions. WRN is primarily involved in DNA repair via nonhomologous end joining (NHEJ) and in DNA replication, H3K9 methylation, and telomere regulation (Croteau et al., 2014; Zhang et al., 2015b; de Renty and Ellis, 2017). BLM and RecQL4 are necessary for proper homologous recombination (HR) and DNA replication (Smeets et al., 2014; de Renty and Ellis, 2017). Together the RecQ diseases highlight how variations in DNA maintenance create distinct pathologies. Whereas ablation of RecQ function irrespective of isoform increases susceptibility to cancer, the differences in aging phenotypes are more nuanced (i.e., premature onset vs. developmental abnormalities).

Similar to NHEJ and HR, mutations in the nucleotide excision DNA damage repair pathway (NER) result in the premature aging disorders xeroderma pigmentosum (mutations in global NER), Cockayne syndrome (mutations in transcription-coupled NER; Mitchell et al., 2015), and trichothiodystrophy (mutations in the transcription factor IIH complex; Stefanini et al., 2010). How defects in NER cause progeroid and neurological pathologies as well as a reduced lifespan are poorly understood (Stefanini et al., 2010; Wilson et al., 2016). Nevertheless, the decreased life expectancy resulting from mutations in the NER pathway and the RecQ helicases strongly implicate DNA damage repair as a contributor to the aging phenotype. However, a caveat is revealed by defects in components of the DNA damage signaling and repair cascade such as ATM protein kinase (McKinnon, 2012) and the Fanconi anemia complex (Taniguchi et al., 2002) which lead to cancer, neurodegeneration, or microcephaly, but not premature aging. Together this set of disorders highlight that defective DNA damage signaling is insufficient to cause progeria, but the type and extent of damage are important determinants of disease pathology.

In support of an involvement of telomere maintenance in aging, mutations in several telomere regulatory proteins (i.e., TERT, TERC, DKC1, and TIN2, among others) lead to dyskeratosis congenita (Opresko and Shay, 2017). This monogenic telomere disease is hallmarked by genetic anticipation, where the lifespans of mutation carriers decrease with succeeding generations. Furthermore, telomere length has repeatedly been correlated with human morbidity in large cohort studies examining physiological aging (Blackburn et al., 2015). In addition, persistent DNA damage can disproportionately affect telomeres and telomere-associated repair foci increase with age (Hewitt et al., 2012). This telomere-specific damage has been reported to be irreparable, driving cellular senescence, and presumably contributing to organismal aging (Fumagalli et al., 2012). Intriguingly, fibroblasts derived from patients with dyskeratosis congenita have been shown to express progerin, further establishing the link between telomere attrition, senescence, and regulation of the nuclear lamina (Cao et al., 2011a).

An exception to the nuclear-based progeroid diseases is a mouse model with spontaneous mutations in mitochondrial DNA induced by homozygous expression of a proofreading-deficient catalytic subunit of mtDNA polymerase (*POLG*; Trifunovic et al., 2004; Kujoth et al., 2005; Bratic and Larsson, 2013). These mice have respiratory chain dysfunction and mitochondrial damage, coinciding with a shortened lifespan along with premature occurrence of alopecia, anemia, cardiomyopathy, kyphosis, reduced fertility, as well as hearing, hair, and weight loss. Although no corresponding naturally occurring human mutations are known, increased mitochondrial mutations are thought to occur during human aging (Bratic and Larsson, 2013). Current evidence indicates that stem cells are particularly sensitive to mitochondrial dysfunction (Hämäläinen et al., 2015), implying that rapid embryonic stem cell depletion may contribute to the premature aging phenotype (Ahlqvist et al., 2012, 2015). Curiously, mice with mutations in the mitochondrial DNA helicase Twinkle also display an accumulation of mtDNA mutations but do not exhibit premature aging symptoms (Tynismaa et al., 2005). Hence, despite the dramatic phenotype, how mtDNA polymerase dysfunction causes premature aging remains poorly understood. One avenue may be through a number of mechanisms for mitochondrion–nucleus cross talk (Sahin et al., 2011; Cagin and Enriquez, 2015; Li et al., 2016; Lionaki et al., 2016; Quirós et al., 2016). However, if nuclear (dys)function contributes to the pathology in these models has not been examined.

defects until progerin is reexpressed upon differentiation into mesenchymal stem cells (MSCs; Liu et al., 2011; Zhang et al., 2011b; Miller et al., 2013; Chen et al., 2017). Together, these studies implicate lamin A variants in HGPS and, most likely, in physiological aging.

Sequestration at the nuclear periphery in the aging process

The observation that HGPS and RD are caused by mutations that directly affect nuclear lamina proteins points to the nuclear periphery as a potential contributor to premature, and possibly normal, aging. Notably, expression of lamin A variants has been detected in physiological models of aging such as extensively passaged normal human fibroblasts and vascular smooth muscle cells, fibroblasts from centenarians, aged-patient skin biopsies, and sections from coronary arteries (Cao et al., 2007; McClinck et al., 2007; Rodriguez et al., 2009; Olive et al., 2010; Ragnauth et al., 2010; Lattanzi et al., 2014). In addition, many of the cellular defects observed in HGPS, such as elevated levels of DNA damage and telomere dysfunction, are the primary causes of other premature aging disorders (see text box), potentially placing the nuclear periphery upstream of these processes. Several observations in multiple premature aging disorders suggest that sequestration of proteins at the nuclear periphery, or loss thereof, may be responsible for prominent defects associated with premature and physiological aging. In particular, peripheral regulation appears to affect several key features of aging including impaired cell stemness, dysregulated cytotoxicity, and

increased senescence, as well as aberrant chromatin structure and telomere stability.

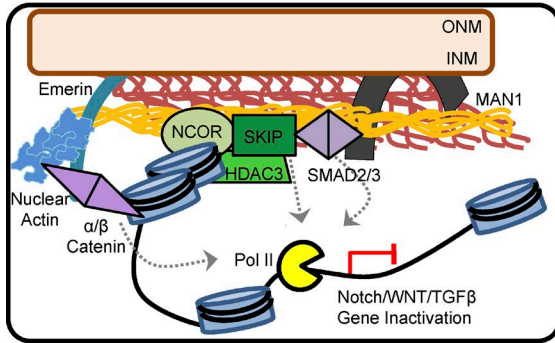
Cell stemness

The regenerative potential of many tissues declines with age, contributing to dysfunction and degeneration (López-Otín et al., 2013). Although the progressive loss of stem cell function by a number of different stimuli has been associated with aging, HGPS models have highlighted that dysregulation of the pathways governing stem cell fate can likewise contribute to stem cell exhaustion and the aging phenotype (Scaffidi and Misteli, 2008; Rosengarten et al., 2011).

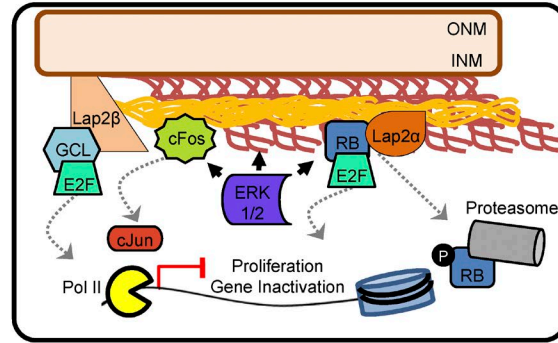
Notch. Notch activation regulates proliferation, migration, and differentiation and is critical in stem cell homeostasis (Conboy et al., 2003, 2005; Bjornson et al., 2012; Balistreri et al., 2016; Bray, 2016). Activation of the Notch receptor induces cleavage of the intracellular domain of the transmembrane receptor and translocation into the nucleus, where it interacts with transcriptional activators and repressors (Balistreri et al., 2016; Bray, 2016). In physiological aging, loss of Notch signaling prevents stem cell renewal in muscle and contributes to cardiovascular anomalies, whereas elevated Notch signaling can lead to cancer and promotes inflammation via nuclear factor- κ B, MAPK, and TGF β (Balistreri et al., 2016).

Progerin expression in human MSCs causes activation of Notch target genes and results in the loss of stem cell identity and differentiation defects (Scaffidi and Misteli, 2008). Interestingly, gene activation occurs in the absence of induction of the

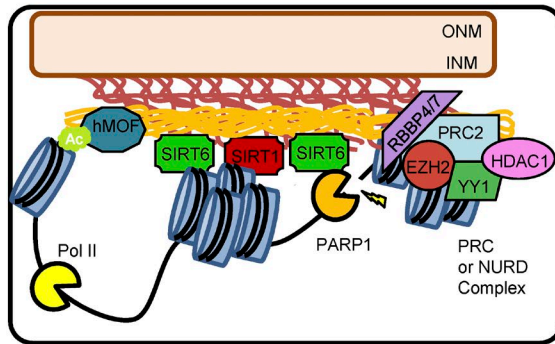
A Cell Stemness



B Proliferation



C Chromatin Regulation



D Telomere Maintenance

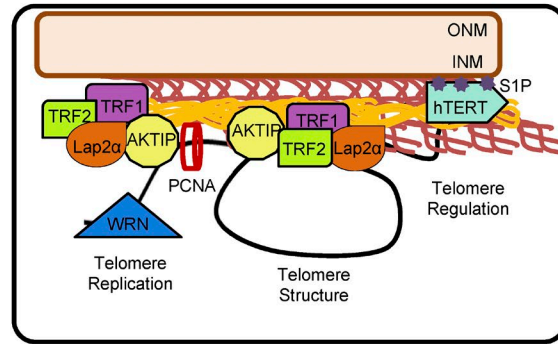


Figure 2. Mechanisms of protein sequestration at the nuclear periphery. (A) The INM regulates cell stemness via sequestration of Notch, Wnt, and TGF β pathway effectors. The Notch signaling corepressor NCOR and coactivator SKIP are anchored to the nuclear periphery in normal cells (Zhang et al., 2003; Demmerle et al., 2012). Although NCOR is activated at the nuclear periphery, SKIP may be restricted from binding to Notch-dependent promoters. SKIP has also been shown to interact with SMAD2/3 to regulate TGF β -dependent transcription (Leong et al., 2001). Similarly, SMAD2/3 is bound to MAN1. The interaction with MAN1 sequesters SMAD2/3, attenuating heterodimerization with Smad4 and suppressing TGF β -induced transcription (Lin et al., 2005; Pan et al., 2005). Wnt pathway regulation involves emerin-mediated nuclear export of β -catenin as well as the possible stabilization of β -catenin by α -catenin and nuclear actin (Markiewicz et al., 2006; Holaska and Wilson, 2007; Tilgner et al., 2009; Stubenvoll et al., 2015; Serebryanny et al., 2017). (B) Proliferation is regulated by the interaction of the nuclear lamina with AP-1, Rb, and ERK1/2. Hypophosphorylated cFos and Rb are sequestered by the nuclear lamina, priming a readily available population of transcription factors for rapid cell cycle regulation (González et al., 2008; Rodríguez et al., 2010). Activation and nuclear translocation of ERK1/2 contribute to the phosphorylation of Rb and cFos. Phosphorylated Rb is degraded, freeing E2F to activate transcription. Similarly, phosphorylation of cFos facilitates dimerization with cJun and promoter binding. E2F is also sequestered to the nuclear periphery via its interaction with Germ cell-less (GCL) and Lap2 β (Nili et al., 2001). Nuclear ERK1/2 can bind to lamin A/C as well (Rodríguez et al., 2010), potentially regulating its activity and turnover. (C) Lamin A is required for the proper localization and enzymatic activity of SIRT1 and SIRT6, regulating chromatin condensation and poly(ADP-ribose) polymerase 1 (PARP1) activity (Liu and Zhou, 2013; Ghosh et al., 2015). hMOF localization is also dependent on lamin A/C (Füllgrabe et al., 2013), implicating the nuclear lamina in both histone acetylation and deacetylation. In addition, lamin A binds the chromatin remodeling complexes PRC and NuRD, establishing a repressive heterochromatin state at the INM (Pegoraro et al., 2009; Cesarini et al., 2015). (D) The shelterin complex components TRF1/2 and AKTIP regulate telomere replication, length, and stability (Ludérus et al., 1996; Dechat et al., 2004; Wood et al., 2014; Chojnowski et al., 2015). Whereas TRF1 may bind lamin B (Crabbe et al., 2012), TRF2 stabilization of telomeres at the nuclear periphery is dependent on binding to lamin A/C and Lap2 α (Chojnowski et al., 2015). Similarly, AKTIP interacts with lamin A/C, lamin B, and PCNA to regulate telomere replication and stability (Burla et al., 2016). The INM-incorporated lipid moiety S1P is also able to promote telomere stability by preventing the degradation of hTERT (Panneer Selvam et al., 2015).

upstream portions of the pathway, consistent with the nuclear progerin protein being the driver of these effects. Mechanistically, progerin expression reduces levels of nuclear receptor corepressor (NCOR) and increases levels of the Notch pathway coactivator, SKI-interacting protein (SKIP; Zhou et al., 2000; Scaffidi and Misteli, 2008). NCOR and SKIP are anchored to the nuclear periphery in normal cells (Zhang et al., 2003; Demmerle et al., 2012; Fig. 2 A). NCOR is activated when sequestered to the nuclear periphery (Demmerle et al., 2012), whereas SKIP may be restricted from binding to Notch-dependent promoters. The increase in Notch signaling upon progerin expression coincides with SKIP relocation from the periphery and into the nucleoplasm (Scaffidi and Misteli, 2008). Release of SKIP is thought to allow promoter binding, leading to the

observed increases in Notch pathway activation and stem cell depletion (Scaffidi and Misteli, 2008). However, it is uncertain to what extent changes in the INM localization of other Notch cofactors, e.g., sirtuin 1 (SIRT1) or polycomb repressive complex (PRC), alter signaling (Bray, 2016). In support of a role for Notch dysregulation in HGPS, mice expressing progerin have altered wound healing and reduced stem cell function (Rosen-garten et al., 2011), indicative of premature stem cell differentiation. Hence, nuclear defects that accrue with aging may hasten stem cell depletion and enrich for a Notch-insensitive population by altering peripheral regulation of NCOR/SKIP.

Wnt. In conjunction with Notch, the Wnt pathway regulates the balance between stem cell proliferation and differentiation (Brack et al., 2007, 2008; Clevers and Nusse, 2012;

Borggreve et al., 2016). Wnt hyperactivation triggers accelerated cellular senescence (Liu et al., 2007), and aberrant Wnt signaling leads to cancer (Clevers and Nusse, 2012). In the cytoplasm, β -catenin is continuously degraded or maintained at adherens junctions. Upon Wnt receptor activation, β -catenin translocates into the nucleus, where it regulates transcription via lymphoid enhancer binding factor (LEF), T cell factor, and chromatin remodeling (Lien and Fuchs, 2014; McCrea and Gottardi, 2016). The nuclear β -catenin complex also mediates the DNA damage response (Zhang et al., 2011a; Serebryanny et al., 2017) and oxidative stress sensitivity (Essers et al., 2005) and maintains telomerase levels (Hoffmeyer et al., 2012). Expression of progerin or a truncated form of lamin A reduces nuclear β -catenin/LEF1 levels, contributing to defective ECM synthesis and proliferation arrest (Hernandez et al., 2010). Similarly, mice knocked out for *Zmpste24* have a defect in proliferation caused by decreased β -catenin levels (Espada et al., 2008), and mice deficient for LEF1 have defects in regulating bone formation (Noh et al., 2009), supporting a role for the Wnt pathway in HGPS and aging.

Although lamin A expression and nuclear β -catenin levels are correlated (Bermeo et al., 2015), how lamin A regulates β -catenin remains unclear. One mechanism may be through the INM protein emerin (Fig. 2 A), which facilitates β -catenin export from the nucleus (Markiewicz et al., 2006; Tilgner et al., 2009; Stubenvoll et al., 2015). Both lamin A and progerin interact with emerin (Kubben et al., 2010; Chojnowski et al., 2015). Although lamin A, nesprin-2, and protein 4.1R retain emerin at the INM (Zhang et al., 2005; Kubben et al., 2010; Meyer et al., 2011; Wu et al., 2014), its enrichment at the nuclear periphery appears decreased in progerin-expressing cells (Kubben et al., 2010; Eisch et al., 2016). It is tempting to speculate that mislocalization of emerin may impede proper β -catenin signaling. Alternatively, emerin binding to β -catenin at the INM may prevent β -catenin degradation. Both emerin and β -catenin also interact with nuclear actin (Holaska and Wilson, 2007; de Lanerolle and Serebryanny, 2011; Daugherty et al., 2014; Serebryanny et al., 2017; Fig. 2 A), and the interaction with nuclear actin may tether and stabilize the complex selectively to lamin A but not progerin (Simon et al., 2010). It is also possible that β -catenin/LEF1 may be regulated indirectly via other INM-associated proteins such as Yin Yang 1 (YY1), which binds lamin A/C and positions chromatin at the nuclear periphery (Harr et al., 2015). YY1 also directly binds the LEF1 promoter and represses its transcription (Yokoyama et al., 2010). Therefore, changes to the nuclear periphery may alter YY1 activity and consequently LEF1 levels. Regardless of the mechanism, these observations suggest that the nuclear periphery regulates the effectiveness of Wnt pathway signaling.

TGF β . TGF β signaling promotes stem cell proliferation and renewal in a context-dependent manner (Watabe and Miyazono, 2009). Canonical TGF β activation causes the phosphorylation and nuclear translocation of Smad2/3 transcriptional modulators, heterodimerization with Smad4, and chromatin binding (Watabe and Miyazono, 2009; Zhang, 2009). However, Smad proteins also signal via other pathways. In bone marrow-derived adult human MSCs, Smad3 activation induces nuclear translocation of β -catenin to promote proliferation and prevent differentiation (Jian et al., 2006). In differentiated mouse embryonic fibroblasts, TGF β inhibits proliferation by dephosphorylating retinoblastoma protein (Rb) in a lamin A/C-protein phosphatase 2A (PP2A)-dependent manner (Van Berlo et al.,

2005). Lamin A/C also facilitates dephosphorylation of Smad2 by PP2A, suggesting that the nuclear periphery mediates TGF β -induced proliferation (Van Berlo et al., 2005).

Although it is not known how these interactions are altered in HGPS, patients with mutations in another INM protein, MAN1, are symptomatic for patches of abnormally increased bone density and disseminated patches of connective tissue including osteopoikilosis, Buschke–Ollendorff syndrome, and melorheostosis, which are associated with increased TGF β signaling (Hellemans et al., 2004). Similar to lamin A/C, MAN1 binds phosphorylated Smad2/3 (Lin et al., 2005; Pan et al., 2005; Fig. 2 A). Binding to MAN1 reduces Smad2/3 phosphorylation, prevents heterodimerization with Smad4, alters the nuclear localization of activated Smad2/3, and ultimately suppresses TGF β -induced transcription. Intriguingly, microarray analysis suggests that TGF β signaling in fibroblasts derived from old individuals closely resembles that of cells derived from HGPS patients (Aliper et al., 2015).

The reactive oxygen species (ROS) response

With age, mitochondria lose their respiratory activity because of a buildup of oxidative damage, propagating a cycle of increasing oxidative stress and mitochondrial dysfunction (Bratic and Larsson, 2013; López-Otín et al., 2013; Ahlqvist et al., 2015). Accumulation of ROS can trigger loss of protein function, aberrant activation of signaling pathways, and the accumulation of DNA damage (Bratic and Larsson, 2013). As in physiological aging models, HGPS cells exhibit signs of mitochondrial dysfunction and increased ROS levels (Kubben et al., 2016; Xiong et al., 2016), implicating signaling from the nuclear periphery in mitochondria homeostasis.

Nuclear factor erythroid 2-related factor 2 (Nrf2)

Nrf2 is a transcriptional activator of a global cytoprotective response to reduce chemical and oxidative stress (Ma, 2013). Nrf2 is continuously degraded by the actin-bound Keap1/Cul3 ubiquitin ligase complex. When redox-sensitive cysteine residues in Keap1 are modified, Nrf2 is released and translocates into the nucleus to transcriptionally regulate autophagy, inflammasome activation, ER stress, and the unfolded protein response, as well as mitochondrial redox signaling (Ma, 2013). Nrf2 levels change with age in a tissue- and model-dependent manner (Zhang et al., 2015a). Yet it is poorly understood whether Nrf2 levels are increased in response to higher ROS damage with age or decreased as the capacity to respond to stress is impaired with age. This is further complicated by regulation of Nrf2 by multiple signaling factors including Notch (Wakabayashi et al., 2014), c-Myc, and DNA damage proteins (Zhang et al., 2015a). Nevertheless, given the long-standing hypothesis that unregulated ROS production contributes to physiological aging (Harman, 1956), Nrf2 may be a major contributor to the aging phenotype.

In HGPS fibroblasts, Nrf2 is improperly sequestered to the nuclear periphery by progerin, reducing its nucleoplasmic concentration and impairing Nrf2-dependent transcription (Kubben et al., 2016). In contrast, mutations in lamin A that cause various muscular dystrophies induce Nrf2 nuclear translocation and transcriptional activation (Dialynas et al., 2015). Hence, although some lamin A mutants are able to induce Nrf2 signaling, progerin impairs the Nrf2-mediated response to oxidative stress by sequestration. This finding explains why HGPS models have increased ROS levels and mitochondrial dysfunction (Viteri et al., 2010; Peinado et al., 2011; Richards

et al., 2011; Rivera-Torres et al., 2013; Kubben et al., 2016; Xiong et al., 2016). Because this effect may be stressor dependent (Hashimoto et al., 2017), it will be important to determine whether Nrf2 is sequestered at the nuclear lamina in physiological aging.

Octamer-binding transcription factor 1 (Oct-1).

Oct-1 regulates several transcriptional pathways, including the cellular stress response, and represses aging-related collagenase genes (Imai et al., 1997; Malhas et al., 2009; Zhao, 2013). Similar to Nrf2, cellular stress stabilizes Oct-1 and promotes cell survival (Zhao, 2013). A fraction of nuclear Oct-1 associates with lamin B1 at the nuclear periphery (Kim et al., 1996; Malhas et al., 2009; Columbaro et al., 2013). Intriguingly, increasing the passage number of a preimmortalized cell line results in the loss of lamina-retained Oct-1 and increased collagenase gene expression (Imai et al., 1997). The JNK-dependent association of Oct-1 with lamin B1 has been estimated to differentially regulate 57 genes, many of which are involved in the oxidative stress response (Malhas et al., 2009; Boubriak et al., 2017). Knockdown of either Oct-1 or lamin B1 increases ROS accumulation and sensitivity to oxidative stress, whereas co-knockdown increases cell survival (Malhas et al., 2009; Shimi et al., 2011). Conversely, duplication of the *LMNB1* gene in adult-onset autosomal dominant leukodystrophy, a disease characterized by the progressive degradation of myelin, increases sequestration of Oct-1 at the nuclear periphery (Columbaro et al., 2013). Therefore, retention of Oct-1 by lamin B1 may be a means to restrict Oct-1 binding to chromatin. Alternatively, peripheral Oct-1 may aid in recruiting genomic regions to the nuclear lamina; however, Oct-1 knockout does not appear to affect the interaction between lamin B1 and chromatin (Meuleman et al., 2013). Further studies should determine whether loss of lamin B during senescence or in HGPS affects the localization and activity of Oct-1, and what downstream impact this interaction has on ROS accumulation and the aging phenotype.

Proliferation

The inhibition of proliferation and accumulation of senescent cells has been strongly suggested to cause an age-associated decline in function via triggering of secretion of a set of inflammatory cytokines, growth factors, and interleukins, referred to as senescence-associated inflammatory/secretory phenotype, as well as the depletion of stem and progenitor cells (van Deursen, 2014; Childs et al., 2015; Baker et al., 2016). The nuclear periphery, in concert with a series of intricate checkpoints and signaling pathways, regulates the proliferative potential of the cell, as evidenced by the induction of senescence in HGPS models (Varela et al., 2005).

Rb. Cellular stressors such as DNA damage, hypoxia, and ROS activate the tumor suppressor protein p53 (Lasry and Ben-Neriah, 2015). p53 subsequently activates p21, and unresolved stress leads to downstream activation of p16INK4A and inhibition of the kinases CDK2, CDK4, and CDK6 (Childs et al., 2015; Lasry and Ben-Neriah, 2015). Inhibition of these cyclin-dependent kinases prevents Rb phosphorylation, facilitating the interaction of unphosphorylated Rb with and inhibition of the E2F transcription factors. This regulatory mechanism prevents damaged cells from proliferating by inhibiting cell cycle progression, alters transcription of a large number of gene targets including the RecQ helicases (Yamabe et al., 1998; Dimova and Dyson, 2005; Liu et al., 2008), and induces cellular senescence (Lasry and Ben-Neriah, 2015).

Hypophosphorylated Rb is sequestered via lamin A/C and Lap2 α (Mittnacht and Weinberg, 1991; Templeton et al., 1991; Mancini et al., 1994; Kennedy et al., 2000; Markiewicz et al., 2002; Johnson et al., 2004; Pekovic et al., 2007; Fig. 2 B). The lamin–Rb interaction prevents complex degradation in a SUMO-dependent manner (Johnson et al., 2004; Sharma and Kuehn, 2016) and promotes further TGF β -mediated Rb dephosphorylation (Van Berlo et al., 2005). It remains uncertain whether sequestration of unphosphorylated Rb also withdraws E2F to prevent transcription or whether Rb sequestration increases E2F signaling by impeding the E2F–Rb interaction (Nitta et al., 2006; Pekovic et al., 2007); however, current evidence suggests that lamin A/C acts to restrict proliferation (Johnson et al., 2004; Nitta et al., 2006; Naetar et al., 2008; Rodríguez et al., 2010). Furthermore, the lamin–Rb complex may exist in the nucleoplasm bound to Lap2 α as well as at the periphery (Naetar et al., 2008; Rodríguez et al., 2010), and the function of these two pools remains a point of interest. Regardless, the nuclear retention of lamin A/C and stabilization of hypophosphorylated Rb likely prime a readily available population of Rb for rapid cell cycle regulation (Nitta et al., 2006). Similar to Rb, another E2F repressor termed Germ cell-less is tethered to INM-localized Lap2 β . Germ cell-less is proposed to bind and recruit E2F to the periphery, preventing E2F-dependent transcription (Nili et al., 2001; Fig. 2 B).

In fibroblasts derived from HGPS patients, cell cycle dysfunction correlates with altered Rb signaling (Dechat et al., 2007; Marji et al., 2010), despite hyperactivation of p53 (Varela et al., 2005; Liu et al., 2006; Kudlow et al., 2008; Wheaton et al., 2017). Similar to HGPS, fibroblasts derived from normally aged elderly individuals exhibit signs of increased progerin expression and a respective decrease in Rb levels (Han et al., 2008; Marji et al., 2010). Therefore, progerin, unlike lamin A/C, may not protect Rb from degradation, causing the Rb pools to be exhausted too quickly. Furthermore, whereas Rb binding to the nuclear lamina regulates proliferation, release of Rb from the lamina may facilitate inhibitory binding of Rb with E2F on promoters, causing global changes in chromatin conformation and inducing senescence-associated heterochromatin foci (Narita et al., 2003). This process may be mediated via loss of lamin B1 (Shimi et al., 2011; Sadaie et al., 2013) and partially parallels the changes in chromatin organization that occur in HGPS (Chandra et al., 2015). Although multiple studies have confirmed the lamin–Rb interaction, and it is clear that Rb plays a critical role in proliferation, how the lamin–Rb complex contributes to aging warrants further study.

Activating protein 1 (AP-1). The transcription factors Fos and Jun heterodimerize to form the AP-1 complex (Eferl and Wagner, 2003). c-Fos and c-Jun respond to mitogenic signals to translocate into the nucleus and promote cell cycle progression by activating transcription of cyclins and repressing p53 and p16INK4A (Eferl and Wagner, 2003). AP-1 is regulated by many of the pathways discussed here, including Notch (Chu et al., 2002), Wnt (Lien and Fuchs, 2014), TGF β (Verrecchia et al., 2001), and NRF2 (Zhang et al., 2015a). As with Rb, lamin A/C is able to bind dephosphorylated c-Fos at the nuclear periphery, preventing heterodimerization with c-Jun and chromatin binding (Ivorra et al., 2006; González et al., 2008; Fig. 2 B). In response to mitogenic signals, ERK1/2 is phosphorylated and, in turn, increases expression of c-Fos and c-Jun (Eferl and Wagner, 2003). ERK1/2 also phosphorylates c-Fos to release it from the nuclear periphery, activating AP-1 transcription (González et al., 2008).

Notably, ERK1/2 interacts with lamin A/C as well, which may facilitate efficient activation of cotethered c-Fos, or lamin A/C may sequester ERK1/2 in a dormant state at the periphery. In support of the latter hypothesis, decreased lamin A/C expression correlates with increased ERK1/2 activation (Muchir et al., 2009b), and a mutation in the N terminus of lamin A/C that leads to Emery–Dreifuss muscular dystrophy exhibits increased ERK1/2 signaling (Muchir et al., 2007, 2009a). Interestingly, lamin A/C binds ERK1/2 and Rb in a mutually exclusive manner: activation of ERK1/2 dislodges lamin A/C-bound Rb at the nuclear periphery, promoting Rb phosphorylation, degradation, and cell cycle activation (Rodríguez et al., 2010; Fig. 2 B). In this way, as increasing ERK enters the nucleus, more Rb is dislodged from lamin A/C and degraded (Rodríguez et al., 2010). Similarly, more c-Fos is phosphorylated and released from lamin A/C (González et al., 2008). Both processes work together to induce proliferation. As lamin A/C becomes unbound from Rb and c-Fos, increasing amounts of ERK could be tethered to the lamina as a feedback mechanism to attenuate ERK signaling.

Proliferating cell nuclear antigen (PCNA).

PCNA is a necessary component of the DNA replication machinery and has roles in DNA damage repair and telomere stability (Vannier et al., 2013; Choe and Moldovan, 2017). PCNA expression decreases with age (Goukassian et al., 2000), and delayed induction of PCNA in aged rats may contribute to the accumulation of DNA damage (Kaneko et al., 2002). Indeed, a homozygous missense mutation in *PCNA* causes premature aging, likely induced by increased DNA damage sensitivity (Baple et al., 2014). Furthermore, PCNA interacts with lamins (Shumaker et al., 2008), BAF (Montes de Oca et al., 2009), and the helicase WRN (Lebel et al., 1999). A- and B-type lamins are thought to aid in the localization of PCNA (Shumaker et al., 2008), and disruption of the nuclear lamina using lamin mutants or progerin causes sequestration and aggregation of PCNA, interfering with replication (Spann et al., 1997; Moir et al., 2000; Hilton et al., 2017; Wheaton et al., 2017). Likewise, expression of prelamin A or progerin causes PCNA dysfunction, leading to stalled replication forks that become double-stranded breaks upon collapse (Cobb et al., 2016; Hilton et al., 2017; Wheaton et al., 2017). The impaired proliferation, increased DNA damage, and destabilized telomeres found in HGPS, physiological aging, and PCNA dysfunction implicate PCNA as a potential mediator of both physiological and pathological aging.

Chromatin remodeling

Changes in histone-modifying enzymes have been observed to correlate with lifespan in a wide range of organisms (López-Otín et al., 2013; Zane et al., 2014). Yet little is known regarding the relationships between the array of different chromatin remodeling enzymes and their effects on longevity. Nevertheless, given the importance of the nuclear lamina in genome organization, it is unsurprising that HGPS and senescing cells undergo a drastic remodeling of the chromatin landscape that correlates with changes in the nuclear lamina (Shah et al., 2013; Chandra et al., 2015).

SIRT6s. SIRT6s are a family of NAD-dependent deacetylases, which have diverse roles in metabolism, cancer, and aging (López-Otín et al., 2013). SIRT1 and SIRT6 regulate longevity via their roles in genomic stability, metabolic regulation, and chromatin modification (Liu and Zhou, 2013). SIRT1 binding to

lamin A, but not progerin or prelamin A, properly activates SIRT1 (Liu and Zhou, 2013; Fig. 2 C). SIRT1 is also responsible for autophagy-mediated deacetylation of histone H4K16 (Füllgrabe et al., 2013), linking a full autophagy response to lamin A expression. Whereas SIRT1 decreases H4K16ac levels, hMOF, an acetyl transferase that increases H4K16ac, is down-regulated upon autophagy induction (Krishnan et al., 2011; Füllgrabe et al., 2013). hMOF has also been shown to bind to lamin A but not prelamin A, and this interaction facilitates localization to the nuclear periphery (Krishnan et al., 2011). Although the role of the hMOF–lamin A interaction in autophagy is unknown, lamin A may coordinate proper H4K16 acetylation. Similar to aged cycling fibroblasts (Zane et al., 2014), prelamin A–expressing cells are hypoacetylated at H4K16 (Krishnan et al., 2011), which correlates with defects in DNA damage repair and premature senescence. Determining how the balance between SIRT1 and hMOF activity is regulated by the nuclear lamina may give valuable insights into the peripheral regulation of heterochromatin and euchromatin.

SIRT6 deacetylates several histone lysines on histone H3, including on aa position K9, K27, K18, and K56, to aid in DNA damage repair (Zane et al., 2014) as well as prime telomeres for WRN binding (Tasselli et al., 2017). SIRT6 also represses expression of embryonic stem cell transcription factors, in addition to targets of the AP-1 complex, and coactivates NRF2 (Sundaresan et al., 2012; Pan et al., 2016; Tasselli et al., 2017). Like SIRT1, SIRT6 binding to lamin A, but not progerin, increases enzymatic activity (Ghosh et al., 2015). Lamin A is necessary for SIRT6 recruitment to DNA damage and proper chromatin interaction (Fig. 2 C). However, in HGPS models, SIRT6 activity and expression are reduced, which may contribute to the defects in DNA damage repair, chromatin organization, and telomere maintenance (Endisha et al., 2015; Ghosh et al., 2015). Although the role of peripheral versus nucleoplasmic lamin A is still in question, these studies demonstrate that controlled expression of lamin A is critical for proper function of SIRT1 and SIRT6.

Histone methylation complexes. Retinoblastoma binding protein (Rbbp)4/7 are members of the nucleosome remodeling and deacetylase (NuRD) complex and the polycomb repressive complex 2 (PRC2; Laugesen and Helin, 2014). These complexes are generally responsible for heterochromatin maintenance and both Rbbp4 and 7 bind lamin A and BAF, but not progerin (Montes de Oca et al., 2009; Pegoraro et al., 2009; Fig. 2 C). Indeed, cells derived from HGPS patients or fibroblasts from elderly individuals show reductions in Rbbp4/7, HP1γ, and HDAC1 levels. In HGPS cells, these reductions correlate with loss of heterochromatin (H3K9me3) and increased susceptibility to DNA damage (Pegoraro et al., 2009). Rbbp4 also regulates nuclear import, and loss of Rbbp4 induces senescence (Tsujii et al., 2015). Therefore, lamin A may maintain heterochromatin at the nuclear periphery by stabilizing the Rbbp4/7 complex, facilitating proper chromatin organization and nuclear function. (Figs. 1 A and 2 C).

PRC2 has also been found to interact with lamin A, and this interaction is necessary for its proper localization (Cesarini et al., 2015). For example, in undifferentiated myoblast cells, PRC2 is recruited with the *Mx1* homeoprotein and *MyoD* to the nuclear periphery (Wang et al., 2011). PRC2 relocation increases H3K27me3 marks at the periphery and represses the associated muscle-specific differentiation factors. In contrast, HGPS fibroblasts exhibit altered H3K27me3 deposition, loss of

heterochromatin, and changes in gene expression comparable to those of senescent cells (Shumaker et al., 2006; Bracken et al., 2007; McCord et al., 2013; Shah et al., 2013; Chandra et al., 2015). The decrease in histone methylation is likely a result of changes to the peripheral lamin A–PRC/EZH2 interaction (Wang et al., 2011; McCord et al., 2013; Harr et al., 2015). Along the same paradigm as NCOR/SKIP regulation, these studies suggest that chromatin remodeling factors are recruited to the nuclear periphery to invoke a repressive environment, whereas transcription factors are synergistically sequestered at the periphery to limit their activity.

Telomere maintenance

The well-established correlation between telomere length and longevity suggests that progressive attrition of telomeres with iterative cycles of replication causes DNA ends to become exposed, triggering DNA damage and cellular senescence (López-Otín et al., 2013). Telomeres in lower eukaryotes localize to the nuclear periphery (Gonzalez-Suarez et al., 2009), but only a subpopulation of telomeres are peripheral in human cells, and this localization may be sensitive to the proliferative state as well as lamin organization (Ludérus et al., 1996; Gonzalez-Suarez et al., 2009; Arnoult et al., 2010; Crabbe et al., 2012; Chojnowski et al., 2015; Guidi et al., 2015). Although the factors governing telomere positioning in humans remain poorly understood, models of HGPS indicate that the nuclear lamina is important for regulating telomere stability, whereas loss of telomeres may trigger progerin expression (Kudlow et al., 2008; Gonzalez-Suarez et al., 2009; Ottaviani et al., 2009; Cao et al., 2011a; Crabbe et al., 2012; Chojnowski et al., 2015).

Telomere repeat-binding factor (TRF) 2. In vertebrates, TRF1 and 2 bind duplex telomeric DNA as homodimers within the shelterin protein complex to ensure telomere integrity (Wood et al., 2014). TRF1 negatively regulates telomere length and may be localized by lamin B1 to the nuclear periphery during postmitotic nuclear assembly (Crabbe et al., 2012). TRF2 forms protective telomere DNA loops at chromosome ends and at interstitial telomeric sequences. Stabilization of telomeres by TRF2 at the nuclear periphery is dependent on binding to lamin A/C and Lap2 α (Ludérus et al., 1996; Dechat et al., 2004; Wood et al., 2014; Chojnowski et al., 2015; Fig. 2 D). However, TRF2 does not interact with progerin, and cells lacking lamin A/C or cells derived from HGPS patients lose their telomeres (Wood et al., 2014). It remains unclear whether TRF2 no longer binds progerin because of its integration into the periphery or whether there is specific protein–protein disruption. Notably, Lap2 α preferentially interacts with lamin A/C over progerin (Dechat et al., 2000; Kubben et al., 2010), and the levels of Lap2 α (Scaffidi and Misteli, 2006; Vidak et al., 2015) as well as nucleoplasmic lamin A/C are reduced in models of HGPS (Pekovic et al., 2007; Naetar et al., 2008; Chojnowski et al., 2015). The reduction in Lap2 α levels upon progerin expression may inhibit TRF2 binding to lamin A/C. While progerin expression promotes telomere attrition via dysregulated TRF2, expression of a dominant-negative TRF2 protein induces uncapping of telomeres and correlates with increased progerin production (Cao et al., 2011a). Additionally, TRF2 expression is reduced in response to DNA damage in models of adult-onset progeroid syndromes caused by *LMNA* mutations (Saha et al., 2013), potentially propagating DNA damage and p53-mediated

senescence. These data suggest a model in which proper interactions with the nuclear periphery are important for TRF2 function and telomere stability, whereas TRF2 expression may be inhibited across aging disorders by unregulated DNA damage, potentially triggering progerin expression.

AKT-interacting protein (AKTIP). AKTIP, a recently discovered component of the shelterin complex, binds TRF1, TRF2, and PCNA to facilitate telomeric DNA replication as well as regulate telomere stability (Burla et al., 2015). AKTIP is strongly localized at the nuclear periphery in a lamin A–dependent manner, where it transiently interacts with telomeres (Burla et al., 2015, 2016; Fig. 2 D). In HGPS models, the peripheral localization of AKTIP is lost (Burla et al., 2016). Depletion of AKTIP causes cells to senesce, and senescence corresponds with increased prelamin A expression and nuclear deformities (Burla et al., 2015, 2016). This regulatory loop sheds new light on how changes in the nuclear periphery lead to telomere dysfunction, and conversely, how shortened telomeres affect the nuclear periphery.

Sphingosine-1-phosphate (S1P). Not only is the protein composition of the INM important for telomere maintenance, but nuclear lipid moieties may also play a role (Panneer Selvam et al., 2015). S1P binds human telomerase reverse transcription (hTERT) at the nuclear periphery, preventing hTERT degradation and in turn promoting telomere stability (Fig. 2 D). Expression of an hTERT mutant that is unable to bind S1P prevents hTERT localization to the nuclear periphery, and consequently this mutant is rapidly degraded. S1P stability is correlated with delayed senescence in primary cells and increased tumor growth in a xenograft model. Whereas S1P specifically binds and prevents hTERT degradation (Panneer Selvam et al., 2015), TRF2 stabilizes the telomere structure (Wood et al., 2014) and AKTIP facilitates proper telomere replication (Burla et al., 2015). Irrespective of these distinct mechanisms, the nuclear periphery appears to play a protective role in telomere regulation.

Concluding remarks

The disproportionate number of aging disorders caused by mutations in nuclear pathways is striking and illustrates the importance of nuclear homeostasis for the aging process. One general mechanism for how the cell nucleus contributes to aging appears to be the integrity of the nuclear periphery, which is negatively affected by aberrant lamin expression in both pathological and physiological aging. As demonstrated in the cited examples, a likely mechanism for how nuclear function contributes to aging is by altered sequestration of cellular factors at the nuclear periphery. Disrupting the nuclear periphery by mutant lamina proteins has wide-ranging consequences at the structural, signaling, and transcriptional levels. Not only is peripheral regulation important in aging as noted here, but these principles may also apply to cancer, nuclear envelopathies, and other diseases. Although the pathways highlighted in our discussion suggest a role for nuclear sequestration as a basic regulatory principle, many questions remain as to how this process mechanistically inhibits protein function and to what degree it may be generalized. It will be important to determine a complete proteomic description of lamina-associated proteins in various diseases and, although many of the relevant observations are based on correlation, it will be essential to demonstrate that sequestration or loss thereof has functional consequences in aging-relevant pathways.

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