



# Genomic instability and innate immune responses to self-DNA in progeria

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**Abstract** In the last decade, we have seen increasing evidence of the importance of structural nuclear proteins such as lamins in nuclear architecture and compartmentalization of genome function and in the maintenance of mechanical stability and genome integrity. With over 400 mutations identified in the *LMNA* gene (encoding for A-type lamins) associated with more than ten distinct degenerative disorders, the role of lamins as genome caretakers and the contribution of lamins dysfunction to disease are unarguable. However, the molecular mechanisms whereby lamins mutations cause pathologies remain less understood. Here, we review pathways and mechanisms recently identified as playing a role in the pathophysiology of laminopathies, with special emphasis in Hutchinson Gilford Progeria Syndrome (HGPS). This devastating incurable accelerated aging disease is caused by a silent mutation in the *LMNA* gene that generates a truncated lamin A protein “progerin” that exerts profound cellular toxicity and organismal decline. Patients usually die in their teens due to cardiovascular complications such as myocardial infarction or stroke. To date, there are no efficient therapies that ameliorate disease progression, stressing the need to understand molecularly disease mechanisms that can be targeted therapeutically. We will summarize data supporting that

replication stress is a major cause of genomic instability in laminopathies, which contributes to the activation of innate immune responses to self-DNA that in turn accelerate the aging process.

**Keywords** Lamins · DNA damage · Genomic instability · Progeria · Replication stress · Innate immune response · cGAS-STING pathway

## Introduction

Lamins are intermediate filament proteins that form a scaffold between the inner nuclear membrane and chromatin, which is known as the nuclear lamina. Two types of lamins form the nuclear lamina: A-type lamins (lamin A and C), encoded by the *LMNA* gene via alternative splicing, and B-type lamins (lamin B1, B2, and B3), encoded by *LMNB1* and *LMNB2* genes (Burke and Stewart 2013). Cryo-electron tomography shows that nuclear lamins assemble into tetrameric filaments that appear as globular-decorated fibers of 3.5-nm thickness (Turgay et al. 2017). The nuclear lamina is viewed as a center for the organization and distribution of genome function in cells, through its interaction with chromatin, transcription factors, nuclear envelope proteins, nuclear pore complexes, and the cytoskeleton (Guillin-Amarelle et al. 2018). Cells devoid of all lamins exhibit frequent, prolonged, and often nonhealing nuclear membrane ruptures, in addition to increased DNA damage ( $\gamma$ H2AX foci) (Chen et al. 2018). Structurally, lamins consist of a central  $\alpha$ -helical rod domain flanked by

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non-helical globular and tail domains (Burke and Stewart 2013). Lamin A is synthesized as a prelamins A precursor that undergoes extensive processing. In particular, its C-terminal –CAAX motif is farnesylated, the –AAX residues cleaved, and the terminal –Cys residue carboxyl methylated. Subsequently, the last 15 amino acids are cleaved by the Zmpste24/FACE1 metallopeptidase, producing mature lamin A (Schreiber and Kennedy 2013). In addition, lamin A/C are phosphorylated at multiple residues during interphase, which promotes filament disassembly and solubilization into the nucleoplasm (Kochin et al. 2014; Torvaldson et al. 2015). Alterations in the maturation of lamin A result in cellular damage and are associated with disease. Lamin-related diseases or laminopathies embody a range of tissue pathologies, including muscular dystrophies, peripheral neuropathies, lipodystrophies, dermatopathies, leukodystrophies, and segmental progeroid syndromes such as Hutchinson Gilford Progeria Syndrome (HGPS), Atypical Werner Syndrome (AWS), and Restrictive Dermopathy (RD) (Worman et al. 2009; Gordon et al. 2014; Gonzalo and Kreienkamp 2015; Vidak and Foisner 2016; Ho and Hegele 2019). In addition to pathogenic mutations, altered expression levels of lamins are associated with cancer. In particular, reduced lamin A levels have been reported during the progression of a variety of cancers, including breast, ovarian, and cervical cancers, often associated with poor prognosis (Alhudiri et al. 2019; Wang et al. 2019).

Hutchinson Gilford Progeria Syndrome (HGPS) is caused by a single-base substitution in exon 11 of the *LMNA* gene that activates a cryptic splice site, leading to deletion of 50 residues near the C-terminus that include the Zmpste24 cleavage site (De Sandre-Giovannoli et al. 2003; Eriksson et al. 2003). The mutant protein, known as “progerin”, remains permanently farnesylated and carboxyl methylated and causes nuclear alterations similar to those of prelamins A-expressing cells. Progerin elicits, in a dose-dependent manner, nuclear deformation, loss of heterochromatin from the nuclear periphery, telomere shortening, deregulation of gene expression, mitochondria dysfunction, oxidative stress, DNA damage, and eventually premature entry into senescence (Goldman et al. 2004; Merideth et al. 2008; Pereira et al. 2008; Prokocimer et al. 2013; Gordon et al. 2014; Gonzalo and Kreienkamp 2015; Ullrich and Gordon 2015; Kreienkamp et al. 2016; Gonzalo et al. 2017). Despite

the progress identifying cellular processes altered by progerin, we still lack a clear picture of the molecular mechanisms involved.

HGPS patients are normal at birth but exhibit a clear growth defect by 2 years of age, often not surpassing 4 ft of height and 30 kg of weight (Gordon et al. 2007; Kieran et al. 2007). Before their teenage years, patients show severe aging phenotypes, including almost complete alopecia, swollen veins, age spots, beak-shaped nose, shrunken chin, narrow chest, swollen and stiff joints, reduced fat and bone mineral density, and severe cardiovascular disease (CVD) (Merideth et al. 2008; Gordon, Gordon et al. 2011; Gordon et al. 2014; Ullrich and Gordon 2015). HGPS patients ultimately die at an average age of 14.6 years from cardiovascular complications such as stroke or myocardial infarction (Ullrich and Gordon 2015). The recent finding that progerin is expressed in the hearts of patients with dilated cardiomyopathy and correlates with left ventricular remodeling (Messner, Ghadge et al. Messner et al. 2018) supports a potential role of progerin in CVD during aging. Interestingly, HGPS pathology spares the central nervous system (CNS). Kids with progeria have normal brain function, with no evidence of cognitive or memory challenges usually associated with aging. Studies aiming to understand why cognitive functions in HGPS patients are preserved revealed that the *LMNA* gene in brain produces primarily lamin C and not lamin A or progerin. This is due to the expression of a micro RNA, miR-9, which specifically targets prelamins A/progerin transcripts in the brain (Jung et al. 2012; Jung, Tu et al. Jung et al. 2014). Importantly, expression of miR-9 in HGPS patient-derived fibroblasts alleviates cellular phenotypes of aging. Thus, miR-9 could be considered as a potential strategy to reduce progerin toxicity in different tissues, once all its targets are carefully examined.

Over the years, different mouse models of the disease have been generated, which have been instrumental for identifying mechanisms underlying premature aging and for testing therapies. A mouse model carrying the same mutation as in human patients in homozygosis (*Lmna*<sup>G609G/G609G</sup>) recapitulates more closely the phenotypes of HGPS patients, although with less severity (Osorio et al. 2011). Interestingly, our recent studies revealed that when these mice are fed high-caloric/high-fat diets, they experience a significant extension of lifespan, which is accompanied by increased disease severity (Kreienkamp et al. 2018a). These progeria mice

on high-fat diet recapitulate more closely pathologies of HGPS patients, and thus might represent a better model to study the disease moving forward. Progeria mice and cells derived from HGPS patients are the focus of extensive research to identify molecular mechanisms underlying progerin-induced cellular toxicity and organismal decline, as well as to test therapies that ameliorate disease progression.

Here, we review new knowledge about how disruption of lamins function, and specially progerin expression, impacts cellular mechanisms that maintain genome integrity. In particular, recent studies show that lamins play a role in DNA replication and that the DNA damage that builds up in lamin-deficient cells is elicited in part by replication fork instability. In addition, we discuss the emerging model that DNA damage caused by exogenous or endogenous sources can be detected by cytosolic sensors of nucleic acids, which in turn activate innate immune responses at the crossroads of aging, cancer, and tumor immunity. Lastly, we bring awareness about the beneficial effects of the hormonal form of vitamin D (calcitriol) ameliorating phenotypes of genomic instability in cells with lamin dysfunction and replication stress.

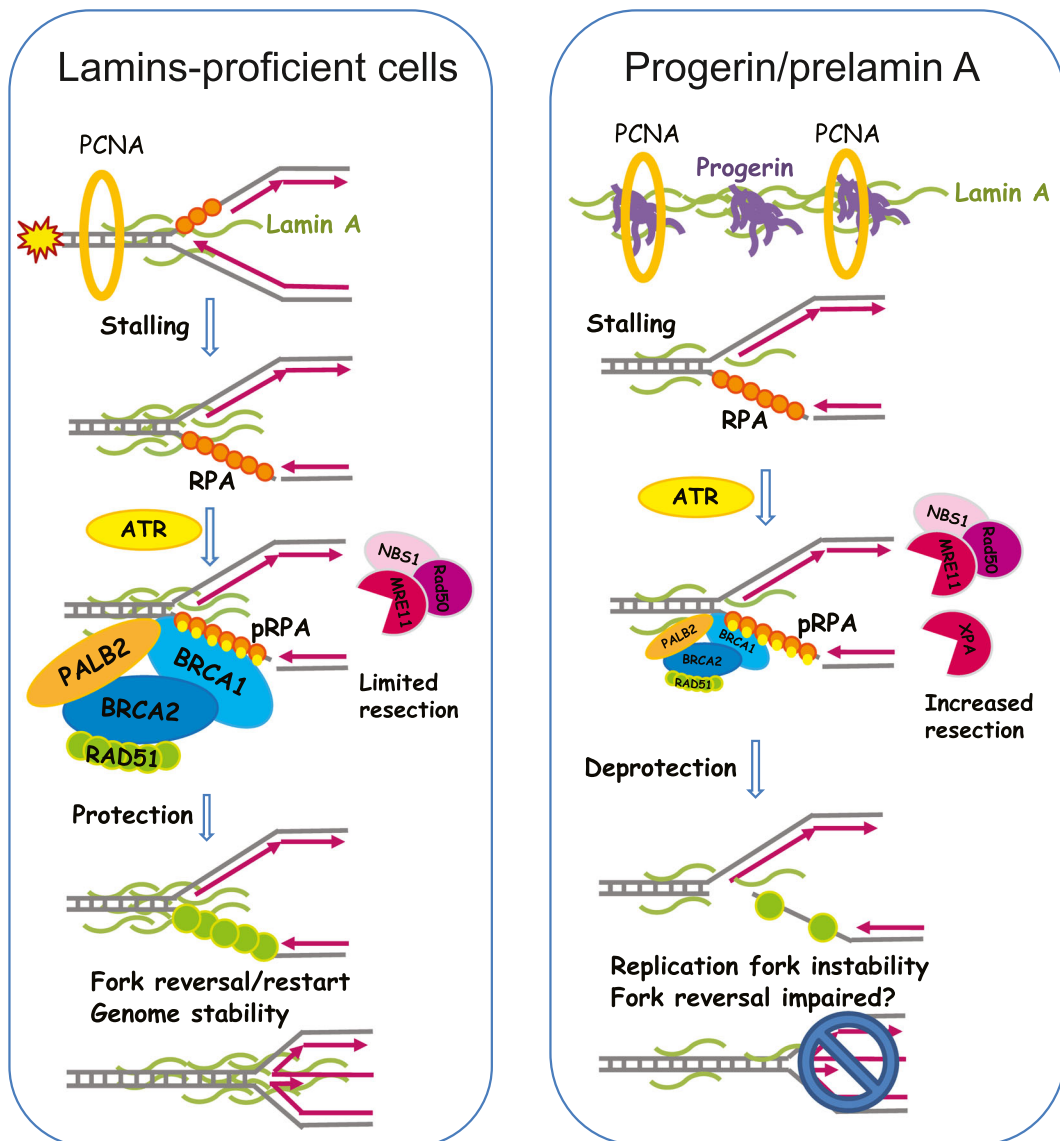
### Lamin dysfunction hinders DNA replication

A whole body of evidence supports that lamin dysfunction, either due to reduced expression or expression of mutants such as progerin, elicits DNA repair defects, telomere dysfunction, and overall genomic instability, reviewed elsewhere (Gonzalo and Kreienkamp 2015; Dobrzynska et al. 2016; Kubben et al. 2016b; Gonzalo et al. 2017; Burla et al. 2018). In recent years, interest in the effect of lamin dysfunction in DNA replication, a stage of special vulnerability for the genome, has been gaining momentum. Early studies in *Xenopus* egg extracts showed that disruption of lamin organization elicits a strong reduction in DNA replication (Spann et al. 1997; Moir et al. 2000). This defect was attributed to changes in the distribution of PCNA and the RFC complex, essential factors in the elongation phase, which formed aggregates with lamins. In mammalian cells, A-type lamins co-localize with PCNA in early sites of DNA replication (Kennedy et al. 2000; Dechat et al. 2008), and a direct interaction between PCNA and lamins via their C-terminus Ig-fold domain seems important for PCNA positioning on chromatin (Shumaker

et al. 2008). In addition, lamins interact with DNA polymerases  $\delta$  (lagging strand) and  $\epsilon$  (leading strand) during S phase (Vaara et al. 2012), and lamin loss is associated with deficiencies in the resolution of stalled replication forks (Singh et al. 2013).

Prelamin A and progerin interact more robustly with PCNA than mature lamin A (Kubben et al. 2010) and are thought to sequester PCNA away from the replication fork, hindering replication fork progression (Wheaton et al. 2017). Consistently, prelamin A expression results in increased mono-ubiquitination of PCNA and induction of Pol  $\eta$ , markers of replication fork stalling (Cobb et al. 2016). In support of the PCNA sequestration model, progerin-expressing cells exhibit a marked reduction of PCNA at replicating DNA (Hilton et al. 2017; Wheaton et al. 2017), concomitant with markers of replication stress/DNA damage such as increased  $\gamma$ H2AX, ATR activation, and RPA Ser33 phosphorylation (Wheaton et al. 2017). Progerin also causes aberrant accumulation of the nuclease XPA at stalled or collapsed forks (Hilton et al. 2017). Lowering the levels of progerin or XPA reinstates normal levels of PCNA at replication forks, with the consequent reduction of cell death. Moreover, RFC1 is degraded by a serine protease in HGPS cells, contributing to deficient loading of PCNA and Pol  $\delta$  onto DNA (Tang et al. 2012). Interestingly, cells carrying other *LMNA* mutations (G232E and Q294P), associated with diseases such as Emery-Dreifuss muscular dystrophy (EDMD), overexpress a HEC-type E3 ubiquitin ligase, HECW2. It was recently shown that HECW2 interacts with PCNA and lamin B1 and mediates their ubiquitination and proteasomal degradation (Krishnamoorthy et al. 2018). HECW2 also interacts and ubiquitinates lamin A, but this interaction is reduced in presence of the mutants. Thus, the functional relationship between lamins, ubiquitinating enzymes, and replication factors should be further investigated as a potential mechanism contributing to genomic instability in laminopathies.

Altogether, these studies provide evidence for lamins playing a role in DNA replication, in part by modulating the association of key proteins such as PCNA to the replication fork, and for expression of prelamin A, progerin, and potentially other lamin mutants, causing replication stress (Fig. 1). In spite of these findings, our mechanistic understanding of lamins' participation in DNA replication is limited. Similarly, the extent to which replication stress contributes to genomic instability in lamin-deficient cells



**Fig. 1** Lamins preserve replication fork (RF) stability. Scheme depicts mechanisms of protection of RF integrity during instances of replication stress (RS) and models how lamin A and progerin impact these mechanisms. Left diagram shows that in lamin-proficient cells, lamin A binds to the RF, together with a broad range of DNA repair and remodeling factors (RPA, BRCA1/2, PALB2, RAD51), helping to ensure the stability of the fork by protecting it from nuclease-mediated degradation. These

protective factors also mediate fork reversal and restart, ensuring genome stability. Right diagram shows a model whereby progerin sequesters PCNA, and potentially wild-type lamin A protein, away from the RF. This, in turn, could lead to RF stalling in addition to RF deprotection and nuclease (MRE11 and XPA)-mediated degradation of the stalled forks. As a consequence, progerin expression causes a robust replication fork instability phenotype

and to the pathophysiology of laminopathies warrants further investigation. One could envision that different mutant lamins, with varying binding affinities for replication factors such as PCNA and DNA polymerases, could cause different DNA replication phenotypes. In addition, lamin dysfunction is associated with DNA repair deficiencies and accumulation

of DNA damage, which poses a challenge for replication fork progression (Berti and Vindigni 2016; Bhat and Cortez 2018). Thus, lamin-deficient cells might need to deal with extra roadblocks that stall the replication fork. Given the increasing evidence that DNA repair proteins interact and protect the replication fork, while helping with the resolution of

replication conflicts (Kolinjivadi et al. 2017), it is feasible that lamin deficiency hinders the recruitment/function of DNA repair factors at the replication fork. Some evidence along this line was obtained recently (Li, Chen et al. 2018). Li and colleagues demonstrated that lamin A binds the homologous recombinase RAD51, preventing its proteasomal degradation. They also identified a lamin-binding ligand (LBL1) that breaks lamin A-RAD51 interaction, rendering RAD51 available for proteasome-mediated degradation, which in turn inhibits DNA repair by HR (Li, Chen et al. 2018). Thus, it is tempting to speculate that loss of lamins or expression of mutant forms might inhibit RAD51 role in DNA replication, causing replication stress. New techniques such as genome-wide single-molecular replication assays (DNA fiber assays), in situ analysis of protein interactions at DNA replication forks (SIRF) (Roy et al. 2018), isolation of proteins on nascent DNA (iPOND) (Sirbu et al. 2011), and electron microscopy (Vindigni and Lopes 2017) are allowing us to identify specific mechanisms during replication that are regulated by lamins, and those that are altered in cells expressing different lamin mutations. Interestingly, there is evidence by iPOND that lamin A, but not progerin, binds to nascent DNA (Wheaton et al. 2017).

We recently used single-molecule replication assays to monitor the impact of progerin expression on DNA replication. We found increased frequency of replication fork stalling in progerin-expressing cells under normal conditions, but not in lamin A-depleted or -overexpressing cells (Kreienkamp et al. 2018b). Replication fork stalling was accompanied by fork deprotection and Mre11 nuclease-mediated degradation. Consistently, inhibition of Mre11 nuclease activity by the compound Mirin rescues progerin-induced replication defects. Replication fork instability was also observed in lamin-depleted cells, but only after treatment with fork-stalling compounds (unpublished results). These replication defects are associated with the increased DNA damage and the chromosomal aberrations characteristic of lamin-deficient cells. Ongoing studies are focused on understanding the molecular mechanisms whereby progerin expression or loss of lamins cause replication fork instability, with emphasis on potential deficiencies in DNA repair factors that stabilize stalled replication forks.

### Activation of innate immune response to self-DNA in progeria

Recent work has established a strong relationship between DNA damage and immune signaling (Chatzinikolaou et al. 2014; Karakasilioti et al. 2013; Brzostek-Racine et al. 2011). DNA damage caused by exogenous sources (genotoxic agents, UV, ionizing radiation) or endogenous metabolic processes (DNA replication, telomere dysfunction, oxidative stress) is sensed in the nucleus by a repertoire of factors that trigger the DNA damage response (DDR) (Ciccia and Elledge 2010). The DDR, as well as other cellular programs such as the unfolded protein response, oxidative stress, senescence, or apoptosis, are coupled with the generation of signals that trigger systemic responses (Galluzzi et al. 2018). DNA damage for instance generates nucleic acid byproducts that can leak into the cytoplasm, where they are recognized by the machinery responsible for the detection of foreign nucleic acids (Kawai and Akira 2006; Ishikawa et al. 2009; Cai et al. 2014). One of the main sensors of cytoplasmic self-DNA and DNA from pathogens is cGAS (cyclic-GAMP synthase), an enzyme that upon binding to DNA synthesizes 2',3'-cGAMP (cyclic-Guanosine MonoPhosphate-Adenosine MonoPhosphate Synthase) from ATP and GTP. cGAMP acts as a second messenger to activate the adaptor protein STING (stimulator of interferon genes), playing a crucial role in antimicrobial immune response (Li and Chen 2018). Upon cGAMP binding, STING is translocated from the ER to the ERGIC/Golgi compartments where it mediates IRF3 and NF- $\kappa$ B activation and nuclear translocation, via kinases TBK1 and IKK, respectively. Nuclear IRF3 and NF- $\kappa$ B induce the expression of type I IFNs and other pro-inflammatory cytokines that boost the immune response. IFNs are then released into the extracellular milieu where in an autocrine or paracrine fashion bind IFN receptors (IFNAR), which through the JAK/STAT pathway activate hundreds of IFN-stimulated genes (ISGs) (Schneider et al. 2014). The role of the cGAS/STING/IFN pathway activating the innate immune system to clear pathogen-infected or damaged cells has been clearly demonstrated (Dou et al. 2017; Gluck et al. 2017; Harding et al. 2017; Yang et al. 2017; Li and Chen 2018). This pathway is also necessary for the establishment of senescence and has been shown to impact anti-tumor immunity and the response of tumors to immunotherapy (Brzostek-Racine, Gordon et al.

2011; Yu et al. 2015; Wang et al. 2017; Ng et al. 2018). Thus, the cGAS/STING/IFN cascade, which is activated in immune cells, tumor cells, and cells in the tumor microenvironment, is currently at the spotlight as a new target for immunotherapy.

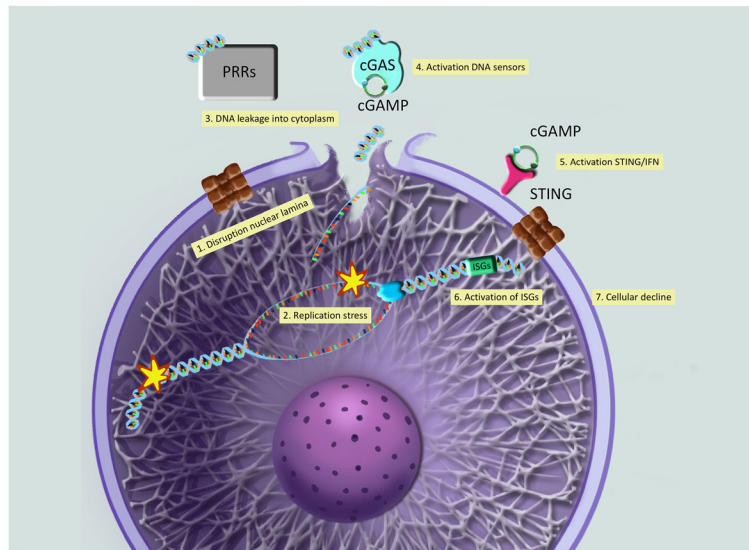
The rapidly growing list of factors that trigger the cGAS/STING/IFN pathway includes carcinogens like DMBA, ionizing radiation, genotoxic agents such as cisplatin and etoposide, oncogenes, DNA repair/replication defects, telomere dysfunction, micronuclei, depletion of ssDNA-binding proteins RPA and RAD51, and loss of the cytoplasmic nuclease TREX-1 or the dNTPase/exonuclease SAMHD1 (West et al. 2015; Chen et al. 2016; Wolf, Rapp et al. Wolf et al. 2016; Bhattacharya, Srinivasan et al. Bhattacharya et al. 2017; Harding, Benci et al. Harding et al. 2017; Mackenzie et al. 2017; Parkes et al. 2017; Coquel et al. 2018; Li and Chen 2018; Ng, Marshall et al. Ng et al. 2018).

Our studies have shown that progerin expression activates the cGAS/STING/IFN pathway (Graziano et al. 2018; Kreienkamp et al. 2018b). Performing genome-wide RNAseq analysis of human skin fibroblasts derived from four HGPS patients and normal fibroblasts from three parents, we identified a robust signature of activation of genes in the IFN/antiviral/innate immunity category. Nearly 50 genes in this category were upregulated in HGPS fibroblasts of early and late passage in culture, compared to normal fibroblasts. These genes included pattern recognition receptors (PRR), proteins that normally survey the cytoplasmic space in search of nucleic acids from pathogens, but that also recognize self-nucleic acids that reach the cytoplasm (RIG-I, MDA5, OASs, PKR, TLR3). In addition, we found upregulation of PRR downstream signaling, including IRFs (IFN responsive factors), STAT1 (signal-transducing activators of transcription 1), and NFkB, as well as over 40 STAT1-regulated IFN-stimulated genes (ISGs). The results of our RNAseq analysis in HGPS fibroblasts were recapitulated upon expression of progerin, but not lamin A, in normal human-derived fibroblasts. In particular, induction of progerin expression rapidly leads to increased protein levels of cGAS and STING, global STAT1 and phosphorylated forms (Y701 and S727), IRF3, and ISG15 (interferon stimulated gene 15), a marker of IFN pathway activation (Graziano et al. 2018; Kreienkamp et al. 2018b). Intriguingly, IFNs themselves were not expressed in HGPS fibroblasts, indicating that this pathway represents a cell-intrinsic, IFN-independent activation of STAT1

downstream inflammatory signals. Activation of STAT1 and downstream ISGs in an IFN-independent fashion has been previously reported in other models (Dempoya, Matsumiya et al. Dempoya et al. 2012; Luu, Greenhill et al. Luu et al. 2014). Interestingly, a recent study showed that STAT1 mediates autoinflammation, lipoatrophy, and juvenile lethality in a mouse model that carries a gain-of-function mutation in the *PDGFRB* (platelet-derived growth factor receptor beta) gene (He et al. 2017). As such, crossing *PDGFRB* mutants with *STAT1*<sup>-/-</sup> mice rescues autoinflammation and improves lifespan. In contrast, deletion of IFNARs does not rescue wasting in these mice, indicating that STAT1 effect driving wasting in this context is independent of IFNs.

Our studies in progerin-expressing cells support a role for STAT1 linking DNA damage sensing with activation of innate immune responses. In particular, knockdown of STAT1 in progeria cells to levels observed in normal cells results in reduced expression of ISGs, in addition to improved cell proliferation and migration capabilities (Graziano et al. 2018; Kreienkamp et al. 2018b). These data suggest that STAT1 activation might contribute to cellular aging phenotypes. Further studies are needed to determine if STAT1 downregulation or pharmacological inhibition ameliorates organismal decline in mouse models of laminopathies, especially in progeria mice. This would be an important finding, given that STAT1 is associated with inflammation in immune and vascular cells during cardiovascular disease (Szelag, Piaszyk-Borychowska et al. Szelag et al. 2016), which underlies early death in HGPS patients (Prakash, Gordon et al. Prakash et al. 2018).

Another question that remains unanswered is the etiology of activation of the cGAS/STING pathway in HGPS. The robust replication fork instability phenotype observed in progerin-expressing cells suggests a model whereby replication stress causes DNA damage, leading to accumulation of nucleic acids in the cytosol that trigger the cGAS/STING pathway (Fig. 2). In support of this notion, immuno-FISH studies with lamin A antibody and a PNA-labeled telomere probe show that HGPS fibroblasts and MAFs from progeria mice accumulate telomeric DNA in the cytoplasm (Kreienkamp et al. 2018b). Given that telomeres are among the most difficult-to-replicate domains, it is likely that cytoplasmic telomeric DNA results from replication defects. However, this hypothesis remains to be formerly tested.



**Fig. 2** Model of how progerin activates innate immune responses to self-DNA. Our recent studies support a model whereby alterations in lamins function (1), such as the case of progerin expression, cause replication stress and genomic instability (2), in addition to disruption of nuclear integrity (1). These two events—increased DNA damage and nuclear fragility/leakage—contribute to the accumulation of DNA byproducts in the cytoplasm, where they are erroneously recognized as foreign

by pattern recognition receptors or PRR (3). One of the key PRR is cGAS (cGAMP-synthase), which through the synthesis of cGAMP (4) activates STING (5) and a STAT1-mediated IFN response. Through transcriptional activation of hundreds of ISGs (6), the cells induce a robust innate immune response to self-DNA, which contributes to cellular and organismal aging (7). *Graphic illustrations generated by Michael Andrus, BS, St Louis University*

Moreover, it is possible that the disruption of nuclear integrity by progerin exacerbates the leakage of DNA into the cytoplasm. Thus, the combination of replication stress/DNA damage and disruption of nuclear integrity might be responsible for the marked activation of the cGAS/STING pathway and the IFN-like response in progeria (Fig. 2).

### Vitamin D (calcitriol) reduces replication stress and represses innate immune response

Our work has revealed unique functions of the vitamin D/vitamin D receptor (VDR) axis maintaining genome stability. VDR loss in normal human fibroblasts immortalized with telomerase results in downregulation of homologous recombination proteins BRCA1 and RAD51, complete loss of recruitment of BRCA1 to DNA damage sites, accumulation of DNA double-strand breaks (DSBs), and premature entry into senescence (Graziano, Johnston et al. Graziano et al. 2016). Interestingly, cells undergoing oncogene (Ras<sup>V12</sup>)-induced senescence exhibit downregulation of VDR

concomitant with reduced expression of DNA repair factors BRCA1 and 53BP1. Treatment with calcitriol (hormonal active form of vitamin D) increases levels of VDR and DNA repair factors and improves DNA repair capabilities (Graziano, Johnston et al. Graziano et al. 2016). We also demonstrated that lamin-depleted and progerin-expressing cells display low VDR expression (Kreienkamp et al. 2016). Calcitriol increases VDR levels and ameliorates progerin-induced cellular phenotypes, including nuclear morphological abnormalities, DNA damage, and premature senescence. Interestingly, calcitriol rescues replication fork instability to the same extent as Mirin treatment in progerin-expressing cells and represses genes in the IFN/antiviral/innate immunity category that are upregulated in HGPS fibroblasts (Kreienkamp et al. 2018b). In particular, we observed reduced global levels of STAT1 and levels of phosphorylated STAT1 upon calcitriol treatment. As testament of the beneficial effects of calcitriol in progeria, treatment of HGPS fibroblasts with calcitriol for 10 days increased their efficiency of reprogramming into iPSCs (induced pluripotent stem cells) (Kreienkamp et al. 2018b). The effect of calcitriol rejuvenating HGPS patient-derived

cells justifies preclinical studies to evaluate the effect of calcitriol in mouse models of progeria, and potentially other laminopathies.

The molecular mechanisms whereby calcitriol ameliorates HGPS cellular phenotypes await further investigation. It is possible that by rescuing replication fork instability, calcitriol reduces the DNA damage and accumulation of cytoplasmic DNA that activates the cGAS/STING pathway and the STAT1-mediated IFN-like response. However, calcitriol also improves nuclear morphological abnormalities, which could enhance the integrity of the nuclear envelope and reduce leakage of nucleic acids into the cytoplasm in HGPS cells. Unraveling how calcitriol rescues replication stress would be of critical importance for laminopathies, and might also provide a strategy to ameliorate replication stress in other contexts. Moreover, calcitriol has been shown to impact directly on STAT1, playing an important role in immune system function (Yang et al. 2013). Calcitriol decreases STAT1 and STAT3 phosphorylation/activation and inflammatory cytokine output in cancer cell lines and autoimmune disease mouse models (Muthian, Raikwar et al. Muthian et al. 2006; Wang, Li et al. Wang et al. 2013; Chen et al. 2015), as well as in large granular lymphocyte leukemia (LGLL) (Kulling et al. 2018; Osorio et al. 2011). Thus, it is possible that the beneficial effect of calcitriol in HGPS is the combination of many factors: (i) improved DNA repair/replication, (ii) reduced nuclear fragility, and (iii) direct downregulation of STAT1/IFN-like response. Studies in the next few years will hopefully shed light onto the relationship between vitamin D/VDR signaling, DNA damage, and immunogenicity of self-DNA.

Importantly, we demonstrated that different compounds known to ameliorate cellular decline in HGPS, also reduced the extent of replication stress and STAT1 activation (Kreienkamp et al. 2018b). These include all-trans-retinoic acid (ATRA), which represses progerin expression (Swift et al. 2013; Pellegrini, Columbaro et al. Pellegrini et al. 2015; Kubben et al. 2016a); Remodelin, an inhibitor of NAT10 (N-acetyltransferase-10) that rescues nuclear abnormalities via microtubule organization; and the combination of lonafarnib, farnesyltransferase inhibitor that inhibits progerin prenylation, and rapamycin, which increases autophagy-mediated progerin clearance (Cao et al. 2011; Gordon, Kleinman et al. Gordon et al. 2016). Overall, the data suggest that these phenotypes—

replication stress and STAT1/IFN response—are drivers of the cellular decline in HGPS. Consistent with this idea, in aged normal human fibroblasts, activation of the STAT1/IFN pathway is concomitant with a decline in fibroblast functionality, including proliferation, differentiation, and migration (Midgley, Morris et al. Midgley et al. 2016). Importantly, progerin and prelamin A expression has been observed in different tissues from normal aged individuals (Dahl, Scaffidi et al. Dahl et al. 2006).

### Concluding remarks

Many lines of evidence point to genomic instability driving cellular decline in lamin-related diseases. DNA replication, in particular, is at center stage as a process that requires an intact nuclear lamina. Although the specific role/s that nuclear lamins play in DNA replication are not fully understood, data suggest that the recruitment of factors critical for DNA replication and for protection of replication forks from degradation is hindered upon nuclear lamin dysfunction. Moreover, evidence of the implication of replication stress and DNA damage in the activation of antiviral/innate immune responses is growing strong. In the context of laminopathies, the characteristic nuclear fragility is likely to contribute to increase the robustness of the response. Importantly, this response has been placed at the crossroads of senescence/aging, cancer, immunosurveillance, and cancer immunotherapy, which illustrates the importance of understanding molecular mechanisms that allow its tunability. We envision that the near future will bring new knowledge also about pharmacological strategies that target this response. For instance, understanding how calcitriol, a hormone produced in our body, modulates genome stability and the innate immune response is of critical importance, and of potential immediate applicability to the clinic. Although still at the infancy of manipulating/tuning these pathways and mechanisms, new technologies and animal models will allow us to advance in ways that help patients with a broad range of diseases.

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