Front. Biol. 2017, 12(1): 49–62
DOI 10.1007/s11515-016-1435-x

REVIEW

Mechanisms of genome instability in Hutchinson-Gilford progeria

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BACKGROUND: Hutchinson-Gilford progeria syndrome (HGPS) is a devastating premature aging disorder. It arises from a single point mutation in the *LMNA* gene. This mutation stimulates an aberrant splicing event and produces progerin, an isoform of the lamin A protein. Accumulation of progerin disrupts numerous physiological pathways and induces defects in nuclear architecture, gene expression, histone modification, cell cycle regulation, mitochondrial functionality, genome integrity and much more.
OBJECTIVE: Among these phenotypes, genomic instability is tightly associated with physiological aging and considered a main contributor to the premature aging phenotypes. However, our understanding of the underlying molecular mechanisms of progerin-caused genome instability is far from clear.
RESULTS AND CONCLUSION: In this review, we summarize some of the recent findings and discuss potential mechanisms through which, progerin affects DNA damage repair and leads to genome integrity.

Keywords HGPS, DDR, DSB repair

Introduction

Maintenance of a stable genome is critical for cells to faithfully pass on the correct genetic information to the next generation. Unfortunately, long chain nucleotide macromolecules that form our genome are constantly threatened by mutagenic origins that arise from both exogenous and endogenous sources (De Bont and van Larebeke, 2004; Gonzalo, 2014). These mutagens include UV light, ionized irradiations, chemical agents, endogenous estrogens, metabolism generated reactive oxygen species (ROS), etc. (De Bont and van Larebeke, 2004; Friedberg et al., 2004; Helleday et al., 2014). Moreover, additional DNA damages can also arise from disruption of cellular activities such as DNA replication, transcription and telomere protection (Mirkin E V and Mirkin S M, 2007; Longhese, 2008; Haffner et al., 2011; Olcina et al., 2013). It is estimated that over 10^5 DNA lesions are created per human cell per day (Gonzalo, 2014), including mispaired DNA bases, pyrimidine dimers, inter-strand cross-links (ICLs), single-strand DNA breaks (SSBs) and double-strand DNA breaks (DSBs) (Ciccia and Elledge, 2010). If improperly or inefficiently handled, these lesions will result in DNA mutations, chromatin deletions or rearrangements and may eventually cause a variety of pathological phenotypes such as tumorigenesis and premature aging (Hoeijmakers, 2009; Gonzalo, 2014). To preserve genome integrity and avoid mutations, cells develop DNA damage response (DDR), a signal transduction pathway mediated by PIKKs family member (primarily ATM, ATR and DNAPKcs), to detect DNA damages and to orchestrate downstream cellular activities (Ciccia and Elledge, 2010). The execution of DNA damage repair mechanisms is stimulated and tightly regulated by DDR (Sirbu and Cortez, 2013). In preparation for DNA damage repair, DDR inhibits cell cycle progression by activating the checkpoint kinases Chk1 or Chk2 (Zhou and Elledge, 2000), which usually become gradually turned off with the repair of DNA damages (Polo and Jackson, 2011). However, under abnormal circumstances upon excessive DNA damages, compromised DDR or misregulated DDR, DNA damage will accumulate in cells to an extent that exceeds their handling capacity and eventually lead to genome instability. To eliminate or restrict unwanted genomes, cells undergo either programmed cell death (apoptosis) or permanent cell cycle arrest (cellular senescence), both of which undermine organismal homeostasis and contribute to physiological aging over time (Norbury and Zhivotovsky, 2004; Roos and Kaina, 2006;

Received August 31, 2016; accepted November 10, 2016
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Chen et al., 2007; Schmitt et al., 2007; d'Adda di Fagagna, 2008; Garinis et al., 2008; Childs et al., 2014). In this regard, genome instability induced by misregulated or defective DDR is widely considered to contribute to the accelerated aging phenotypes in multiple diseases including Werner syndrome (WS), Ataxia telangiectasia (A-T), Fanconi's anemia (FA) and Hutchinson-Gilford progeria syndrome (HGPS) (Oshima et al., 1993; D'Andrea and Grompe, 2003; Garinis et al., 2008; Sahin and Depinho, 2010; Gonzalo, 2014; Brosh et al., 2016).

HGPS is a devastating and ultra-rare premature aging disease, with an estimated incidence rate of 1 in every 21 million of a population (Gonzalo et al., 2016) and data from Progeria Research Foundation). HGPS patients, despite very young, are characterized by a variety of aging associated clinical phenotypes, including loss of subcutaneous fat, loss of hair, bone joint abnormalities and severe cardiovascular disorders (Gordon et al., 2007; Merideth et al., 2008; Capell and Collins, 2016). HGPS patients start to display these features at the age of 12-24 months old and die at an average age of 13-14 years old due to myocardial infarction or stroke (Gordon et al., 2007). Interestingly, unlike many other accelerated aging diseases such as WS, A-T or FA, which are caused by mutations that directly interfere with DDR, most HGPS cases arise from a *de novo* single point mutation in the *LMNA* gene, a gene that mainly encodes two type V intermediate filament proteins: lamin A and lamin C (Oshima et al., 1993; D'Andrea and Grompe, 2003; Eriksson et al., 2003; Capell and Collins, 2006; Mathew, 2006; Lavin, 2008; Musich and Zou, 2009; Zhang et al., 2015). This mutation (C1824T) lies in the exon 11 of the *LMNA* gene and activates a cryptic splice donor site, yielding a 50 amino acid truncated mutant protein termed progerin (Fig. 1) (Eriksson et al., 2003). Progerin lacks an internal Zmpste24 cleavage site and undergoes an abnormal post-translational modification, being permanently farnesylated at the C terminus. This farnesyl tail anchors it to the inner nuclear membrane (INM) and disrupts the structure and function of nuclear lamina meshwork, an important polymeric structure that regulates nuclear morphology, chromatin organization and various cellular processes (Eriksson et al., 2003; Capell and Collins, 2006; Gonzalo, 2014). Progerin accumulation induces multiple pathological phenotypes such as lobulated nuclear morphology, disrupted heterochromatin structure, altered gene expression profile, premature cellular senescence and genome instability (Goldman et al, 2004; Liu et al., 2005; Capell and Collins, 2006; Shumaker et al., 2006; McCord et al., 2013). Among these phenotypes, genome instability is closely related to premature aging, leaving us an important question regarding how progerin perturbs genome integrity (Lombard et al., 2005). Over the past decade, researchers addressed this question from various angles and have achieved significant progress. In this review, we will first briefly describe phenotypes related to genome instability in HGPS and then discuss some of the recent findings to synthesize a set of molecular mechanisms to explain progerin's role in genome instability. Finally, we will summarize current and potential HGPS therapeutic approaches targeting HGPS pathological pathways that include but not limited to genome instability.

Deficiencies in DNA damage responses (DDR) & DNA double-strand break (DSB) repair in HGPS

In this section, we will give a brief introduction about how

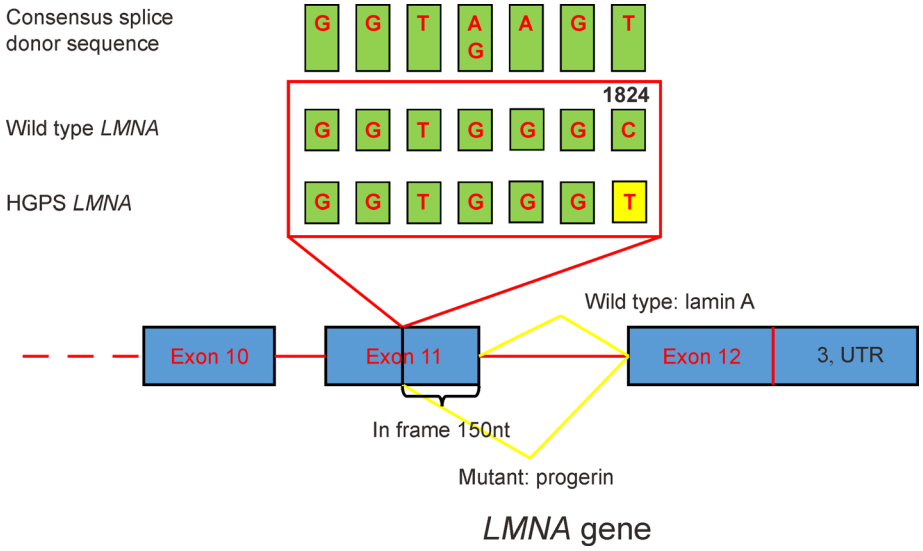

Figure 1 A scheme of the classic HGPS mutation in *LMNA* gene. The consensus splice donor site, wild type and HGPS *LMNA* sequences are shown. The 1824 cysteine in the wild-type *LMNA* gene is mutated into a thymine in HGPS. This mutation creates a cryptic splice donor site in exon 11, which can be recognized by the spliceosome and causes an in-frame deletion of 150 nucleotides. The splicing variant will subsequently yield a mutant protein which bears a 50 amino acid shorter than wild type lamin A.

cells sense, signal and repair DSBs, the most toxic type of DNA damage, followed by listing phenotypes related genome instability in HGPS.

DSBs can be detected by protein sensors such as PARP1/2, the Ku70-Ku80 complex and the Mre11-Rad50-Nbs1 (MRN) complex in a sequence-independent manner (Polo and Jackson, 2011). Once recruited, the MRN complex serves as a scaffold to dock and activate signaling proteins including ATM, the master kinase that phosphorylates and activates a variety of factors involved in DNA damage repair and checkpoint activation (Lee and Paull, 2004, 2005; Gonzalo, 2014). One important substrate of ATM is the histone H2A variant H2AX (Burma et al., 2001). Upon phosphorylation, H2AX turns into γH2AX, a widely recognized DSB marker, and attracts MDC1, which in turn further recruits MRN complex and ATM (Stewart et al., 2003; Chapman and Jackson, 2008; d'Adda di Fagagna, 2008). Additional ATM mediates the phosphorylation of adjacent H2AX molecules, thereby evoking a positive feedback loop and amplifying DDR signals (d'Adda di Fagagna, 2008; Polo and Jackson, 2011). The above signaling process enriches MDC1 at DSBs, which facilitates the recruitment of downstream DSB repair factors (Kolas et al., 2007; Mailand et al., 2007; Kinner et al., 2008; Fradet-Turcotte et al., 2013). Among these factors, BRCA1 and 53BP1 are of significance, given their roles in regulating the balance between the homologous recombination (HR) and the non-homologous end joining (NHEJ) DSB repair pathways (Gonzalo, 2014). HR and NHEJ are the two major DSB repair pathways that antagonize with each other at DSB break ends (Polo and Jackson, 2011; Chapman et al., 2012; Gonzalo, 2014; Gonzalo and Kreienkamp, 2015). HR utilizes sister chromatid as a template to fix DSBs in an error-free fashion, while NHEJ simply rejoins DSB break ends together and therefore is likely to introduce DNA mutations, chromatin deletions or rearrangements (Polo and Jackson, 2011). BRCA1 favors HR by promoting DSB end resection and preparing for downstream homology search, whereas 53BP1 promotes NHEJ and inhibits HR by restricting end resection (Chapman et al., 2012; Zimmermann et al., 2013). As stated above, DDR and DSB repair are highly complex and spatial-temporally regulated cellular responses, and each step is strictly dependent on the previous one. The presence of progerin may disrupt multiple steps during the process via different mechanisms and yield a variety of defective phenotypes.

The defective DSB repair in HGPS cells was initially described by Liu et al. in 2005. In that study, skin fibroblasts from HGPS patients displayed a significantly delayed recruitment of 53BP1 and Rad51, two important players in NHEJ and HR respectively, suggesting a delay of both NHEJ and HR (Liu et al., 2005). Similar delays were also observed in mouse embryonic fibroblasts (MEFs) from Zmpste24$^{-/-}$ mice (a progeroid mouse model which accumulates the unprocessed prelamin A and mimics HGPS phenotypes) (Liu et al., 2005). Consequently, both HGPS fibroblasts and Zmpste24$^{-/-}$ MEFs showed much higher sensitivity to various DNA damage inducing agents such as UV light, camptothecin (CPT), etoposide and mitomycin C (MMC) (Liu et al., 2005). Along with these observations, additional studies reported a basal accumulation of γH2AX foci in HGPS fibroblasts as well as MEFs from *Lmna*^{G609G} mouse (a progeroid mouse model which carries the classic HGPS mutation), potentially due to their delayed DSB repair (Liu et al., 2008; Osorio et al., 2011).

Delays in repair lead to accumulation of DSBs and prolonged activation of upstream DDR signals (Malaquin et al., 2015). This was confirmed by a persistent activation of the ATM/ATR kinases and checkpoint pathways in HGPS cells (Liu et al., 2006; Musich and Zou, 2009). As a result, HGPS fibroblasts displayed a strong activation of Chk1 and Chk2, limited proliferation potential and premature senescence (Liu et al., 2006; Musich and Zou, 2009). Ectopic expression of progerin in HeLa cells has been shown to induce ATR nuclear foci and impair 53BP1 recruitment upon UV light or ciplastin treatment, implying a direct negative impact of progerin on DDR and DSB repair (Manju et al., 2006; Musich and Zou, 2009; Musich and Zou, 2011). Together, the above studies provided strong evidence showing the defects within both DDR and DSB repair in HGPS cells. The rest of this article will separately discuss the molecular mechanisms underlying DSB repair as well as DDR defects in HGPS.

Defective DSB repair in HGPS

Progerin impairs DSB repair by interfering with normal lamin A/C functionality

Over the past several years, researchers started to identify lamin A/C as important players in DSB repair. MEFs from *Lmna*$^{-/-}$ mice displayed elevated accumulation of γH2AX, aneuploidy and increased chromatin breaks, suggesting genome instability (Gonzalez-Suarez et al., 2009; Redwood et al., 2011). Moreover, *Lmna*$^{-/-}$ MEFs also bear increased sensitivity to DNA interstrand crosslinks (ICLs) and replication stress (Singh et al., 2013). When treated with ICL agents, *Lmna*$^{-/-}$ MEFs showed decreased recruitment of the FANCD2 repair factor and delayed γH2AX clearance, accompanied by increased aberrant chromosomes (Singh et al., 2013). Similar defects were also observed upon hydroxyurea-induced replication stress (Singh et al., 2013). In addition, one recent study on murine cells reported that lamin A engaged into chromatin through interacting with histone variant H2AX and stabilized DNA damage repair foci, suggesting a structural role of lamin A in DSB repair (Mahen et al., 2013).

Lamin A/C favors both NHEJ and HR by maintaining their repair protein levels. Depletion or shRNA-induced suppression of lamin A results in cysteine protease Cathepsin L

(CTSL) mediated degradation of the NHEJ promoting factor 53BP1 and transcriptional reduction of BRCA1 and RAD51, two key HR regulators (Gonzalez-Suarez et al., 2009; Redwood et al., 2011). Consequently, deletion of lamin A/C inhibits both NHEJ and HR (Redwood et al., 2011; Singh et al., 2013). Mechanistically, 53BP1 binds to lamin A/C via its Tudor domain in human dermal fibroblasts, suggesting that lamin A/C maintains a nucleoplasmic pool of 53BP1 (Gibbs-Seymour et al., 2015). The transcriptional downregulation of BRCA1 and Rad51 in *Lmna* null cells is mediated by the formation of a p130/E2F4 repressor complex, which is increased upon loss of lamin A (Redwood et al., 2011).

Recent studies performed by Zhou's group highlighted lamin A's capacity to tether a variety of DNA damage response factors to the nuclear matrix. For example, lamin A interacts with and facilitates the nuclear matrix localization of histone acetyltransferase Mof (Krishnan et al., 2011). Mof is an important protein involved in genome integrity maintenance and loss of Mof results in G2/M cell cycle arrest, massive chromatin aberrations and defective repair of DSBs (Li et al., 2010). Lamin A was also shown to interact with and facilitate the localizations and activities of the SIRT1 and SIRT6: two important enzymes involved in genome stability maintenance (Mostoslavsky et al., 2006; Oberdoerffer et al., 2008; Liu et al., 2012; Dobbin et al., 2013; Ghosh et al., 2015). Collectively, the above studies indicated an indispensable role of lamin A/C in DSB repair. Interestingly, mice that harbored a lamin A mutant that lacks exon 9 ($Lmna^{D9/D9}$) showed progeroid phenotypes without apparent defects in DSB repair and genome stability, suggesting that other lamin A mutant might induce premature aging without perturbing genome integrity and also that there were specific domains within lamin A that played a functional role in DSB repair (Das et al., 2013).

Progerin is a dominant negative mutant of lamin A and may disrupt normal lamin A functionality in DSB repair (Schreiber and Kennedy, 2013). For example, unprocessed prelamin A (retains the C terminus farnesyl tail and possesses toxicities similar to progerin) displayed a significantly lower Mof affinity compared to wild-type lamin A (Krishnan et al., 2011). Hence accumulation of prelamin A in $Zmpste24^{-/-}$ MEFs interfered Mof-lamin A interaction, disrupted the retention of Mof at the nuclear matrix and impaired 53BP1 foci formation at DNA lesion (Krishnan et al., 2011). Moreover, prelamin A and progerin were both shown to disrupt the interaction between lamin A and SIRT1. As a result, the subcellular localization and deacetylase activity of SIRT1 were significantly disrupted in $Zmpste24^{-/-}$ MEFs as well as in HGPS fibroblasts (Liu et al., 2012). The presence of progerin also disrupted SIRT6 activation and compromised SIRT6 dependent DSB repair (DNA-PKcs recruitment, CtIP deacetylation, and PARP1 mono-ADP ribosylation) (Ghosh et al., 2015). Taken together, these reports suggest that progerin may jeopardize DSB repair by disrupting the normal lamin A's functionality.

Altered epigenetic modifications impair DSB repair in HGPS

Abnormal heterochromatin structure and histone modifications are both hallmarks of HGPS associated epigenetic alterations. In 2004, Goldman et al. initially revealed a significant loss of peripheral heterochromatin in late passage HGPS fibroblasts (Goldman et al., 2004). Subsequent studies uncovered a variety of altered histone modifications in HGPS fibroblasts and HEK293 cells overexpressing progerin (Shumaker et al., 2006). These alterations include loss of facultative heterochromatin marker histone H3 lysine 27 trimethylation (H3K27me3), loss of pericentric constitutive heterochromatin marker histone H3 lysine 9 trimethylation (H3K9me3) and enrichment of constitutive heterochromatin marker histone H4 lysine 20 trimethylation (H4K20me3) (Shumaker et al., 2006). Using chromatin immunoprecipitation followed by sequencing (ChIP-seq), our group identified genome-wide complex alterations of H3K27me3, which was associated with gene density (McCord et al., 2013). Genome-wide chromosome conformation capture (Hi-C) uncovered a global loss of spatial compartmentalization of chromatin in late passage HGPS fibroblasts, suggesting additional chromatin structure abnormalities (McCord et al., 2013).

In recent years, researchers started to connect the abnormal histone modifications and defective DSB repair in HGPS cells. The general concept was that aberrant histone modifications rendered a more condensed chromatin structure and created a physical barrier preventing efficient DNA repair in HGPS cells. For instance, Krishnan et al. showed that $Zmpste24^{-/-}$ MEFs bear H4K16 hypo-acetylation due to the dissociation of the histone acetyltransferase Mof from the nuclear matrix (Krishnan et al., 2011). As a result, chromatin became more condensed, leading to delayed 53BP1 recruitment upon irradiation induced DSBs. Overexpressing Mof or treating cells with HDAC inhibitor restored normal 53BP1 recruitment and ameliorated the premature senescence phenotype in $Zmpste24^{-/-}$ MEFs (Krishnan et al., 2011).

A more recent study from the same group revealed that unprocessed prelamin A or progerin exhibited an enhanced binding capacity to the H3K9me3 methyltransferase SUV39h1. This protected SUV39h1 from proteasome degradation in $Zmpste24^{-/-}$ MEFs and HGPS fibroblasts, leading to increased accumulation of H3K9me3 (Liu et al., 2013). Interestingly, these findings are contradictory to the previously established knowledge of H3K9me3 loss in HGPS (Shumaker et al., 2006). This discrepancy might reflect the differences regarding the cell donors or cellular passages. Nevertheless, the authors observed a passage dependent reduction of H3K9me3, which was consistent with previous findings (Liu et al., 2013). They speculated that accumulation of H3K9me3 might build up a barrier and block effective DNA damage repair. Notably, depletion of SUV39h1 in $Zmpste24^{-/-}$ mice ($Zmpste24^{-/-}$ $SUV39H1^{-/-}$) was able to significantly reduce H3K9me3, improve DSB repair and

alleviate cellular senescence (Liu et al., 2013). At the organismal level, Zmpste24 and SUV39h1 double knockout mice displayed higher bodyweight, increased bone mass and extended lifespan in comparison to Zmpste24$^{-/-}$ mice (Liu et al., 2013).

In addition to Mof and SUV39h1, progerin also disturbs other chromatin modifiers. For example, HGPS fibroblasts and wild type skin fibroblasts overexpressing progerin both displayed significantly reduced protein levels of the retinoblastoma binding protein 4 and 7 (RBBP4 & RBBP7), both of which are components of the nucleosome remodeling deacetylase (NuRD) complex (Pegoraro et al., 2009). Interestingly, loss of RBBP4 and RBBP7 was able to recapitulate part of HGPS associated phenotypes in non-progeria cells. HeLa cells transfected with RBBP4/7 targeting siRNAs displayed a significant loss of H3K9me3 (Pegoraro et al., 2009). Moreover, normal cells depleted of RBBP4/7 showed increased counts of γH2AX foci at basal level (Pegoraro et al., 2009). These findings suggested that progerin might affect chromatin structure and DSB repair at least partially through downregulating RBBP4 and RBBP7.

Progerin misregulates HR/NHEJ pathway choice

The choice between HR and NHEJ DSB repair pathways is regulated by the interplay between BRCA1 and 53BP1 and is dependent on cell cycle progression (Polo and Jackson, 2011; Chapman et al., 2012; Escribano-Díaz et al., 2013). In G0/G1 phase, 53BP1 promotes NHEJ and inhibits HR by blocking DSB end resection (Chapman et al., 2012; Escribano-Díaz et al., 2013). This is carried out through its interaction with local H4K20me2 around DSBs, which forms a chromatin barrier and blocks DNA resection machinery (Bothmer et al., 2010; Gupta et al., 2014). When cells enter S phase, however, cyclin-dependent kinases (CDKs) phosphorylate the CtBP interacting protein (CtIP), which then binds to BRCA1. The CtIP/BRCA1 complex is able to antagonize with 53BP1, promoting DNA end resection and HR (Escribano-Díaz et al., 2013; Panier and Boulton, 2014). Unlike HR, which carries out homology-based error free DSB repair, NHEJ simply religates DNA break ends and mediates rapid, but error-prone DSB repair (Polo and Jackson, 2011; Chapman et al., 2012). The balance between HR and NHEJ is critical for cells to maintain genome integrity and cellular homeostasis. Misregulation of this process could result in chromatin relocation, genome instability and cell death (Bunting et al., 2010; Patel et al., 2011).

Our recent study pointed out that smooth muscle cells (SMCs) differentiated from HGPS iPSCs displayed a misregulated HR/NHEJ pathway choice, resulting in inappropriate DSB fix and mitotic defects (Zhang et al., 2014). We discovered that there was a strong suppression of HR in HGPS SMCs during S/G2 phase as indicated by an almost complete removal of Rad51 recruitment (Zhang et al., 2014). Moreover, overexpression of progerin elicited a strong downregulation of PARP1, a protein that inhibits NHEJ (Patel et al., 2011; Zhang et al., 2014). PARP1 downregulation and HR deficiency together triggered an over activation of the error-prone NHEJ during S/G2 phase. This was demonstrated by a strong recruitment of 53BP1 in HGPS SMCs upon low dosage (mainly creates DSBs in S/G2 phase) CPT treatment (Ray Chaudhuri et al., 2012; Zhang et al., 2014). As a result, over-activated NHEJ led to chromatin rearrangements, aneuploidy/polyploidy karyotypes, mitotic arrest and eventual mitotic cell death (Zhang et al., 2014). These results provided a molecular mechanism that potentially contributed to the vascular SMC loss phenotype in HGPS (Varga et al., 2006; Zhang et al., 2014). Similar to HGPS SMCs, late passage HGPS fibroblasts also displayed PARP1 downregulation and abnormal HR during S/G2 phase ((Zhang et al., 2014) and unpublished data). As a result, HGPS fibroblasts displayed lagging mitotic chromosomes and micronuclei, confirming a defective mitosis (Cao et al., 2007). Additional results demonstrated the presence of lagging chromosomes in mitotic HeLa cells overexpressing progerin, suggesting a direct involvement of progerin in HGPS mitotic defects (Cao et al., 2007). Consistent with these results, aneuploidy was also observed in bone marrow cells from Zmpste24$^{-/-}$ mice (Liu et al., 2005). Interestingly, although an over-activation of NHEJ in S/G2 phase HGPS SMCs was shown, we didn't see a strong NHEJ activation in S/G2 phase HGPS fibroblasts ((Zhang et al., 2014) and unpublished data). In fact, this NHEJ efficiency was comparable to that in S/G2 phase normal controls, suggesting that the severity of pathway choice disruption is cell type dependent (unpublished data). Moreover, this difference may also explain why we didn't observe apparent cell death in HGPS fibroblasts.

A variety of previous studies reported a delayed recruitment of 53BP1 in HGPS fibroblasts, suggesting a disrupted NHEJ (Liu et al., 2005, 2013a, 2013b; Krishnan et al., 2011). However, we found that NHEJ was over-activated in S/G2 phase HGPS SMCs, raising the possibility that delays of NHEJ were predominantly present in G0/G1 phase. Indeed, we observed a significantly delayed recruitment of RIF1 (a NHEJ promoting protein downstream of 53BP1) in serum synchronized G0/G1 phase HGPS fibroblasts (unpublished data). Delayed NHEJ in G0/G1 phase may result in accumulation of DNA damage, prolonged DDR and premature senescence in HGPS.

Together, the above results implied a complete disruption of HR/NHEJ pathway choice in HGPS (Fig. 2). In G0/G1 phase, the presumably prevailing NHEJ is significantly delayed, causing insufficient DSB repair. In S/G2 phase, HR was drastically impaired whereas NHEJ was over-active (at least in HGPS SMCs), leading to inappropriate error-prone repair of DSBs, chromatin abnormalities, and genome instability.

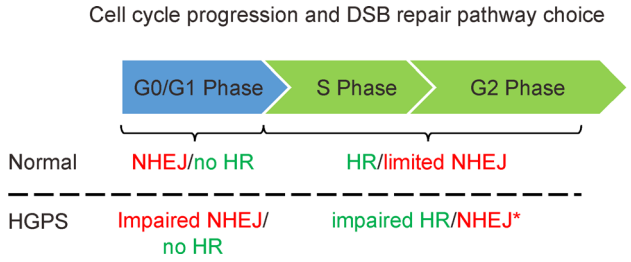

Figure 2 A scheme cell cycle dependent HR/NHEJ pathway choice in normal and HGPS cells. In normal cells: NHEJ is the predominant DSB repair pathway in G0/G1 phase. In S/G2 phase, HR becomes prevalent and antagonizes with NHEJ to limit its effect. In G0/G1 phase HGPS cells: NHEJ is significantly impaired, while HR is completely undetectable. In S/G2 phase HGPS cells: HR is significantly impaired. *: The efficiencies of NHEJ in S/G2 phase HGPS cells may vary between cell types. In S/G2 phase HGPS fibroblasts, NHEJ is similarly effective compared to normal control fibroblasts. In S/G2 phase HGPS SMCs, NHEJ is significantly more effective than that in normal control SMCs.

Disrupted DDR in HGPS

Progerin or unprocessed prelamin A inhibits ATM activation upon DSBs

The ataxia telangiectasia mutated (ATM) is the master regulator in DDR. In response to DSBs, it is recruited by the MRN complex to damaged DNA lesions, where it undergoes self-activation through auto-phosphorylation (Bakkenist and Kastan, 2003; Lee and Paull, 2005). ATM activation requires Nbs1 (a component of the MRN complex) and the histone acetyltransferase Tip60 (Lee and Paull, 2007). Deletion of Tip60 diminished ATM auto-phosphorylation, suggesting that its activity was critical for ATM activation (Sun et al., 2005; Shiloh and Ziv, 2013). Activated ATM then phosphorylates numerous down-stream substrates and orchestrates chromatin remodeling, DNA damage repair and cell fate determination (Shiloh and Ziv, 2013). Deficiencies in ATM usually result in aberrant DNA damage repair, chromatin translocations and genome instability (Tubbs and Sleckman, 2014).

A study from Liu et al. showed that ATM was persistently activated in HGPS fibroblasts at a basal level without additional mutagenic treatment. This further activated Chk2 and led to cell cycle arrest (Liu et al., 2006). Interestingly, in contrast to Liu et al.'s results, a more recent study on Zmpste24 $^{-/-}$ MEFs revealed an attenuated ATM activation in response to ionized irradiation (Liu et al., 2013a). In support of their findings, we also observed a reduced activation of ATM in HGPS fibroblasts treated with doxorubicin (Dox, a topoisomerase II inhibitor), suggesting impaired ATM activation upon DSBs (unpublished data). These conflicting findings were probably due to differential experimental conditions. Liu et al.'s mainly performed their study on HGPS cells without any additional treatment and discovered a basal activation of ATM, which was caused by unrepairable DSBs, whereas we focused on the immediate ATM activation in response to exogenous DSBs ((Liu et al., 2006) and unpublished data). Mechanistically, we found that the defective ATM activation was correlated with progerin accumulation and the loss of H3K9me3 in HGPS fibroblasts (unpublished data). H3K9me3 is an important epigenetic mark, which has been previously shown to recruit Tip60 and activate ATM (Sun et al., 2009). Loss of H3K9me3 by SUV39h1/2 depletion resulted in ATM inactivation, suggesting a critical role of H3K9me3 in ATM activity (Sun et al., 2009). Therefore, we speculate that loss of H3K9me3 may disrupt ATM activation and contribute to genome instability in HGPS.

Progerin disrupts DNA damage induced histone modifications

Upon DSBs, cells carry out a variety of histone modifications (methylation, acetylation, phosphorylation, ubiquitination, etc.) to drive chromatin structure remodeling, DNA break exposure, DDR signal amplification and DSB repair factor recruitment (Bird et al., 2002; Mailand et al., 2007; Kuo and Yang, 2008; Price and D'Andrea, 2013; Ayrapetov et al., 2014). One of the most profound and well-characterized histone modifications upon DSB is the rapid phosphorylation of histone variant H2AX, mediated by PIKKs family members: ATM, ATR or DNAPKcs (Burma et al., 2001; Ward and Chen, 2001; Stiff et al., 2004). γH2AX, MDC1 and ATM create a positive feedback signal amplification loop and serve to recruit and activate downstream DSB repair factors (Paull et al., 2000; Kinner et al., 2008). Another important type of DSB dependent histone modification is the ubiquitination of histone H2A and its variants (Mailand et al., 2007; Mattiroli et al., 2012). RNF8 mediated H2A ubiquitination orchestrates the recruitment of 53BP1 and BRCA1. siRNA-mediated suppression of RNF8 was sufficient to abolish 53BP1 and BRCA1 foci formation upon DSBs (Kolas et al., 2007; Mailand et al., 2007), indicating a critical role of histone ubiquitination in DSB repair. In a more recent study, Ayrapetov et al. (2014) described a transient enrichment of H3K9me3 around DSB breaks. This modification was mediated by a newly defined complex that consists of Kap-1, HP1, and SUV39h1. In their model, SUV39h1 methylates H3K9 around DSBs creating H3K9me3. The nascent H3K9me3 further recruits Kap-1/HP1/SUV39h1 complex through its interaction with HP1 and mediates the methylation of adjacent H3K9, creating a positive feedback loop (Ayrapetov et al., 2014). H3K9me3 recruits histone acetyltransferase Tip60, which down the road acetylates both ATM and histone H4, and promotes DSB repair (Sun et al., 2009; Ayrapetov et al., 2014).

The potential impact of progerin on DSB dependent

histone modifications is under appreciated. Recently, our group demonstrated that there was a passage dependent reduction of γH2AX response in HGPS fibroblasts upon treatment with dox and CPT, suggesting that progerin accumulation might impair γH2AX signals (unpublished data). The reduced γH2AX signal strength was associated with less recruitment of 53BP1 and RIF1, in agreement with its critical roles in DSB repair (Kinner et al., 2008). Consistently, we observed weaker but more persistent γH2AX foci in HGPS fibroblasts. Mechanistically, we found that the weak γH2AX responses were caused by a reduced activation of ATM and loss of H3K9me3 in HGPS fibroblasts (unpublished data), providing a link between the previously established H3K9me3 loss and the DSB repair defects in HGPS. Interestingly, the reduction of ATM activation and γH2AX signals were mainly observed in G0/G1 phase but not in S/G2 phase HGPS cells, providing an upstream mechanism to explain the misregulated NHEJ in HGPS cells (see discussion in the section "Progerin misregulates HR/NHEJ pathway choice").

It has been previously reported that HGPS fibroblasts bear reduced level of the heterochromatin protein 1α (HP1α), a heterochromatin binding protein critical for the maintenance of H3K9me3 (Scaffidi and Misteli, 2005; Shumaker et al., 2006; Zhang et al., 2015). Moreover, HP1α was implied to participate in the transient H3K9me3 modification at DSB break ends. Overexpression of a chromatin domain deleted mutant of HP1α was shown to disrupt the recruitment of Kap-1/HP1/SUV39h1 upon DSBs (Ayrapetov et al., 2014). Thus, although the direct evidence is lacking, reduction of HP1α in HGPS cells may also impair the transient enrichment of H3K9me3 at local DNA lesions and hinder DSB repair.

Progerin disrupts DNA damage-induced chromatin remodeling

A study on Zmpste24$^{-/-}$ MEFs showed that DNA damage triggered chromatin remodeling was impaired by unprocessed prelamin A (Liu et al., 2013a). Due to reduced ATM activation, ATM-dependent phosphorylation of Kap-1 was compromised in Zmpste24$^{-/-}$ MEFs. Un-phosphorylated Kap-1 constantly associates with MNase-resistant heterochromatin and blocks DNA damage-induced chromatin decondensation and remodeling, hindering the recruitment of DSB repair factors (Liu et al., 2013a). siRNA-mediated suppression of Kap-1 was able to rescue the defective chromatin remodeling, improve 53BP1 recruitment and alleviate cellular senescence in Zmpste24$^{-/-}$ MEFs (Liu et al., 2013a).

Progerin undermines genome stability by increasing ROS levels

Genome instability can be triggered either by functional deficiencies in DNA damage repair or by an increased amount of DNA damaging agents. The above discussions mainly focused on progerin's effects delaying DNA damage repair. In this section, we address the potential of progerin to elevate the levels of endogenous DNA damage agents. ROS ($O_2^{-\cdot}$, H_2O_2, $OH\cdot$, etc.) are metabolic byproducts generated during biochemical reactions and are the major endogenous agents accounting for oxidative DNA damage (De Bont and van Larebeke, 2004). By reacting with the double bonds of DNA bases, ROS are able to create more than 20 types of DNA damages including oxidized bases, SSBs and DSBs (Cooke et al., 2003; De Bont and van Larebeke, 2004; Lin and Beal, 2006; Murphy, 2009). Under physiologic conditions, these toxic effects of ROS are antagonized by defense mechanisms such as DNA damage repair. However, oxidative stress will emerge under pathological conditions, when ROS production outcompetes the capacity of cellular defense mechanisms and impairs the intactness of genome (De Bont and van Larebeke, 2004). In 2009, Viteri et al. reported that HGPS cells bear significantly increased accumulation of ROS (1.4 to 4 folds) and oxidatively modified proteins compared to age-matched normal controls. Notably, it seemed that HGPS cells displayed normal levels of ROS scavenging proteins, indicating that progerin affected ROS levels by expanding their origins (Viteri et al., 2010). Elevated ROS in HGPS was later on confirmed by Richards et al. in 2010. Significantly, they found that high levels of ROS were associated with the accumulation of DSBs and the impaired cellular proliferation potential in HGPS fibroblasts (Richards et al., 2011). Moreover, HGPS cells displayed higher sensitivity to oxidative stress as evidenced by inefficient repair of DSBs induced by ROS insults (Richards et al., 2011). Treatment with ROS scavenger N-acetyl cysteine (NAC) alleviated their background DNA damage level and extended their population doubling times, confirming a negative role of ROS in HGPS genome stability (Richards et al., 2011). These findings suggested that progerin might perturb genome stability by introducing extra ROS and sensitizing cells to oxidative stress.

ROS production is tightly correlated with mitochondria functionality (Murphy, 2009). Disruption of mitochondrial function can result in oxidative damage under a variety of pathological situations (Lin and Beal, 2006; Murphy, 2009; Pagano et al., 2014). Studies by our group and others have revealed progerin-induced mitochondrial deficiencies in HGPS fibroblasts (Xiong et al., 2015). To begin with, an SILAC (stable isotope labeling with amino acid) analysis revealed that mitochondrial oxidative phosphorylation proteins were reduced in HGPS patients in comparison to normal subjects (Rivera-Torres et al., 2013). Consistently, mitochondrial ATP synthesis was also found to be reduced HGPS fibroblasts (Viteri et al., 2010; Xiong etal., 2016). Mitochondrial defects were also observed in fibroblasts obtained from adult progeroid mouse models: Zmpste24$^{-/-}$ and *Lmna*$^{G609/G609}$ (Osorio et al., 2011; Peinado et al., 2011). Recently, our group reported that HGPS fibroblasts bear swollen and

fragmented mitochondria (Xiong et al., 2016). Overexpression of progerin in normal fibroblasts was able to recapitulate these abnormal mitochondria, suggesting that progerin negatively impacts mitochondrial integrity and function (Xiong et al., 2016). Our study provided the structural base for HGPS associated mitochondrial defects. Function wise, HGPS fibroblasts and progerin-expressing normal controls displayed significantly delayed mitochondrial movements (Xiong et al., 2016). Moreover, mitochondrial membrane potential (MMP) was shown to be disrupted in HGPS fibroblasts and HGPS-iPSC differentiated SMCs (Xiong et al., 2016). Consistent with previous reports, we observed an obvious elevation of mitochondrial specific ROS in HGPS fibroblasts (Xiong et al., 2015). Together, these findings revealed mitochondria as an important factor that progerin targets to increase cellular ROS.

Progerin affects genome integrity by perturbing DNA replication

The second source of endogenous DNA damage comes from collapsed DNA replication forks (Shrivastav et al., 2008). DNA replication is a fundamental biologic process that allows cells to accurately duplicate their genetic materials (Mazouzi et al., 2014). Replicating genomes are especially susceptible to mutations as endogenous and exogenous agents may threaten their integrity by interfering with the replication fork stabilization, progression, and reestablishment (Branzei and Foiani, 2005; Mazouzi et al., 2014). For example, DSBs may occur due to replication fork collapse when the replication fork encounters DNA lesions (SSBs, inter-strand crosslinks or pyrimidine dimers) (Shrivastav et al., 2008). In this regard, elevated ROS induced by progerin may create DNA lesions on replicating nucleotide chains and introduce DSBs in S phase HGPS cells.

DNA replication is spatial-temporally orchestrated by the replisome, a multiple-component protein complex that consists of replicative helicases, DNA polymerases and their accessory factors such as the clamp loader, replication factor C (RFC) and the clamp itself, proliferation cell nuclear antigen (PCNA) and topoisomerases (Branzei and Foiani, 2010). Given the complexities of this machinery and its functions, it is reasonable to speculate that genetic or functional compromise of its components will negatively affect replication fork and genome stability. Despite lacking direct evidence, several studies implied that progerin or prelamin A may perturb the stability of DNA replication fork machinery (Liu et al., 2008; Musich and Zou, 2009; Tang et al., 2012). For example, Liu et al. reported that the sliding clamp ring protein PCNA formed discrete foci in early passage S phase HGPS cells, but not in late passage HGPS cells, suggesting a redistribution of PCNA occurred during the accumulation of progerin (Liu et al., 2008). PCNA tethers the DNA polymerase δ and ε to ensure rapid DNA synthesis (Kelman, 1997). Its disassociation from the replications forks not only renders unprotected single strand (ss) or double strand (ds) DNA junctions but also inhibits DNA replication, resulting in stalled DNA replication fork and replication fork collapse (Moir et al., 2000; Liu et al., 2008; Musich and Zou, 2009). In this sense, progerin-induced redistribution of PCNA may result in replication fork stalling and subsequent DSBs. This notion was supported by Liu et al.'s finding that xeroderma pigmentosum group A (XPA), a protein with high affinity to ss/ds DNA junctions, was co-localized with DSB marker γH2AX in late passage HGPS cells (Liu et al., 2008). Subsequent studies by Tang et al. discovered that the large subunit of replication factor C (RFC) was proteolytically degraded in HGPS fibroblasts, leading to a truncated RFC of around 75kD and defective loading of PCNA and polymerase δ to the replication fork. These results provided a mechanistic base underlying how progerin perturbed PCNA distribution and introduced DSBs during DNA replication (Tang et al., 2012).

As discussed above, progerin may cause replicative stress by introducing excessive ROS and interfering with replication fork progression. Under physiologic conditions with limited exogenous genotoxic stimuli, endogenous DSBs caused by collapsed replication fork are considered as an important contributor to genome instability. Unfortunately, HR, the predominant DSB repair pathway in S/G2 phase, was found to be disrupted in HGPS cells, implying that HGPS cells were vulnerable to replicative stress induced DSBs (Liu et al., 2005; Zhang et al., 2014). The exact molecular mechanisms underlying the HGPS-related HR deficiency remain unclear. The intermediate single strand DNA structure (ssDNA) generated by replicative fork collapse activates ATR (ATM- and Rad3- related) kinase, which is located to the damaged DNA lesion, triggers DNA damage checkpoint response and facilitates homologous recombination and replication fork restart (Flynn and Zou, 2011). Liu et al. has previously reported that HGPS cells exhibited persistent CHK1 phosphorylation at serine 345 and nuclear ATR foci formation at a basal level, suggesting ATR activation and cell cycle arrest (Liu et al., 2006; Musich and Zou, 2009). However, the above study was performed in unsynchronized cells. It remains unclear whether ATR is able to properly respond to replicative stress and fully carry out its functions in HGPS cells during S/G2 phase. Moreover, we failed to observe ATR activation in HGPS cells in response to Doxorubicin treatment (unpublished data). Therefore, additional studies are required to elucidate ATR activation in HGPS cells upon DNA damage.

Therapeutic approaches to HGPS

Approaches targeting progerin level and toxicity

Progerin retains a permanent farnesyl tail, which anchors it to the INM and triggers a variety of cellular phenotypes. One

classic strategy to neutralize progerin toxicity is to block its farnesylation with farnesyltransferase inhibitors (FITs). Treating HGPS fibroblasts with FTI was able to improve HPGS nuclear morphology (Capell et al., 2005). Moreover, in vivo studies on two HGPS mouse models (BACG608G and $Lmna^{HG/+}$) demonstrated that FTI treatment was sufficient to improve a variety of HGPS associated phenotypes such as short lifespan, growth retardation and bone abnormalities (tested on $Lmna^{HG/+}$) and loss of vascular SMCs (tested on BACG608G) (Varga et al., 2006; Capell et al., 2008; Yang et al., 2006, 2008; Zhang et al., 2013). Significantly, clinical trial on HGPS patients with FTI showed that FTI treatment was able to improve HGPS patients' cardiovascular status and extend the lifespan of HGPS patients by 1.6 years (Gordon et al., 2012, 2014). FTI is by far the most extensively studied and widely applied treatment toward HGPS. It shows considerable beneficial effects on HGPS both *in vitro* and *in vivo*. Suspects on FTI mainly focus on its specificity as it may influence multiple cellular pathways that involve farnesyltransferase. Indeed, FTI treatment was shown to induce centrosome separation defects and causes "donut-shaped" nuclei, calling that attentions should be paid when adopting FTI treatment as a therapeutic strategy (Verstraeten et al., 2011).

The second type aims at reducing the absolute level of progerin and thereby reduce toxicities. One representative of these strategies is the sequence specific morpholino antisense oligonucleotides (AONs), which blocks the cryptic splicing donor site on prelamin A premRNA. Scaffidi et al. showed that AONs were able to improve the nuclear morphology and restore gene expression profile in HGPS fibroblasts (Scaffidi and Misteli, 2005). *In vivo* study performed by Osorio et al. also confirmed the beneficial effects of AONs on $Lmna^{G609G}$ transgenic mice (Osorio et al., 2011). However, attentions should be paid to off-target effects since the dosages of AONs were relatively high (>10 μM) (Scaffidi and Misteli, 2005; Osorio et al., 2011).

In 2011, Cao et al. reported rapamycin, a macrolide-antibiotic, as a promising chemical to reduce the progerin level in HGPS fibroblasts. Mechanistically, rapamycin was able to stimulate the autophagy pathway and remove insoluble progerin aggregates in HGPS cells. In vitro characterization confirmed that rapamycin treatment improved HGPS nuclear morphology, delayed HGPS cellular senescence and promoted HGPS proliferation (Cao et al., 2011). Despite that rapamycin benefits HGPS fibroblasts, *in vivo* studies are necessary to validate its effect on HGPS animal models.

Approaches targeting HGPS genome instability

Genome instability is considered as a driving force of the premature aging phenotypes in HGPS. Thus approaches aiming to maintain genome integrity were also proposed to treat HGPS. One of these methods is to use drugs that target histone modifiers to remove the abnormal epigenetic alterations in HGPS and rescue DSB repair defects. For example, Krishnan et al. showed that HDAC inhibitor sodium butyrate was able to increase H4K16ac, restore 53BP1 recruitment and alleviate premature senescence in $Zmpste24^{-/-}$ MEFs (Krishnan et al., 2011). Another study from the same group proposed that resveratrol was able to enhance SIRT1 activity by reinforcing the interaction between SIRT1 and lamin A (Liu et al., 2012).

Progerin may also induce genome instability by disrupting mitochondrial functionality and increasing oxidative stress (Rivera-Torres et al., 2013). Using ROS scavengers to alleviate intracellular oxidative stress is an alternative way to reduce DNA damage in HGPS. Intriguingly, in our recent study, we showed that methylene blue, a mitochondrial targeting anti-oxidant was able to enhance mitochondrial functionality and reduce ROS levels in HGPS fibroblasts (Xiong et al., 2015). Consequently, methylene blue delayed HGPS premature senescence and significantly extended its proliferation capacity (Xiong et al., 2015).

Conclusion marks

Progerin can be recognized not only as a dominant negative lamin A mutant but also as a gain of function protein, which may impact genome integrity through unknown complex mechanisms. This feature makes mechanistic study especially challenging. Based on our above discussions, mechanisms underlying HGPS genome instability can be divided into three groups: disrupted DDR, defective DSB repair and increased source of DNA damage. These groups can be further sub-categorized according to their specific defects. These defects are associated with lamin A functionality, epigenetic modifications, HR/NHEJ pathway choice, ATM activation; DSB induced histone modifications and chromatin remodeling, ROS balance and DNA replication (Fig. 3). These mechanisms are multi-dimensional but interconnected and together they are reflected on the complex HGPS pathological phenotypes. Despite significant mechanistic advances, important questions remain to be addressed. For example, it is unknown how progerin negatively regulates HR during S/G2 phase. Moreover, how progerin triggers the cell cycle-dependent inactivation of ATM and γH2AX responses is still an open question. Thanks to the mechanistic advances, novel drugs are identified and extremely consummate current FTI based therapy. These approaches mainly target HGPS genome instability and include the adoption of HDAC inhibitors and ROS scavengers. Despite promising, these methods are still under development and additional studies are indispensable to evaluate their effects and risks.

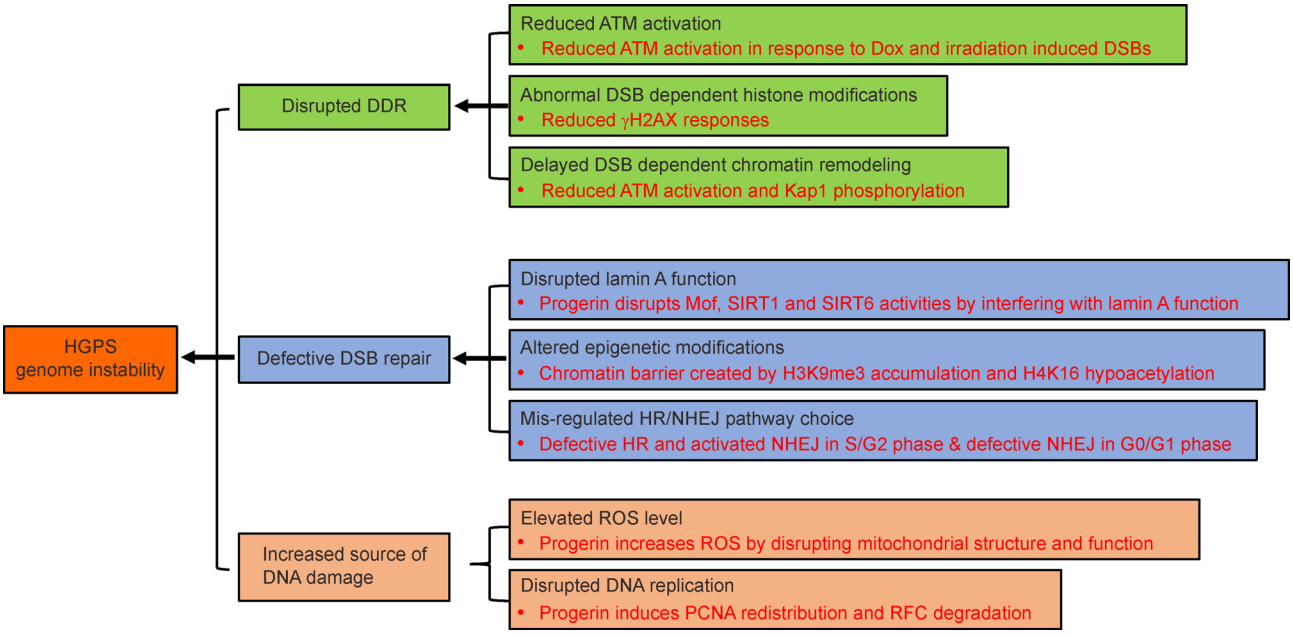

Figure 3 Molecular mechanisms underlying HGPS genome instability. A summary of current molecular mechanisms through which, progerin perturbs HGPS genome integrity. These mechanisms are categorized into three groups: disrupted DDR, defective DSB repair and increased source of DNA damage.

Compliance with ethics guidelines

Haoyue Zhang and Kan Cao declare declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

Ayrapetov M K, Gursoy-Yuzugullu O, Xu C, Xu Y, Price B D (2014). DNA double-strand breaks promote methylation of histone H3 on lysine 9 and transient formation of repressive chromatin. Proc Natl Acad Sci USA, 111(25): 9169–9174

Bakkenist C J, Kastan M B (2003). DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature, 421(6922): 499–506

Bird A W, Yu D Y, Pray-Grant M G, Qiu Q, Harmon K E, Megee P C, Grant P A, Smith M M, Christman M F (2002). Acetylation of histone H4 by Esa1 is required for DNA double-strand break repair. Nature, 419(6905): 411–415

Bothmer A, Robbiani D F, Feldhahn N, Gazumyan A, Nussenzweig A, Nussenzweig M C (2010). 53BP1 regulates DNA resection and the choice between classical and alternative end joining during class switch recombination. J Exp Med, 207(4): 855–865

Branzei D, Foiani M (2005). The DNA damage response during DNA replication. Curr Opin Cell Biol, 17(6): 568–575

Branzei D, Foiani M (2010). Maintaining genome stability at the replication fork. Nat Rev Mol Cell Biol, 11(3): 208–219

Brosh R M Jr, Bellani M, Liu Y, Seidman M M (2016). Fanconi Anemia: A DNA repair disorder characterized by accelerated decline of the hematopoietic stem cell compartment and other features of aging. Ageing Res Rev: S1568-1637(16)30081-2

Bunting S F, Callén E, Wong N, Chen H T, Polato F, Gunn A, Bothmer A, Feldhahn N, Fernandez-Capetillo O, Cao L, Xu X, Deng C X, Finkel T, Nussenzweig M, Stark J M, Nussenzweig A (2010). 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. Cell, 141(2): 243–254

Burma S, Chen B P, Murphy M, Kurimasa A, Chen D J (2001). ATM phosphorylates histone H2AX in response to DNA double-strand breaks. J Biol Chem, 276(45): 42462–42467

Cao K, Capell B C, Erdos M R, Djabali K, Collins F S (2007). A lamin A protein isoform overexpressed in Hutchinson-Gilford progeria syndrome interferes with mitosis in progeria and normal cells. Proc Natl Acad Sci USA, 104(12): 4949–4954

Cao K, Graziotto J J, Blair C D, Mazzulli J R, Erdos M R, Krainc D, Collins F S (2011). Rapamycin reverses cellular phenotypes and enhances mutant protein clearance in Hutchinson-Gilford progeria syndrome cells. Sci Transl Med, 3(89): 89ra58

Capell B C, Collins F S (2006). Human laminopathies: nuclei gone genetically awry. Nat Rev Genet, 7(12): 940–952

Capell B C, Erdos M R, Madigan J P, Fiordalisi J J, Varga R, Conneely K N, Gordon L B, Der C J, Cox A D, Collins F S (2005). Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci USA, 102(36): 12879–12884

Capell B C, Olive M, Erdos M R, Cao K, Faddah D A, Tavarez U L, Conneely K N, Qu X, San H, Ganesh S K, Chen X, Avallone H, Kolodgie F D, Virmani R, Nabel E G, Collins F S (2008). A farnesyltransferase inhibitor prevents both the onset and late progression of cardiovascular disease in a progeria mouse model. Proc Natl Acad Sci USA, 105(41): 15902–15907

Chapman J R, Jackson S P (2008). Phospho-dependent interactions between NBS1 and MDC1 mediate chromatin retention of the MRN

complex at sites of DNA damage. EMBO Rep, 9(8): 795–801

Chapman J R, Taylor M R, Boulton S J (2012). Playing the end game: DNA double-strand break repair pathway choice. Mol Cell, 47(4): 497–510

Chen J H, Hales C N, Ozanne S E (2007). DNA damage, cellular senescence and organismal ageing: causal or correlative? Nucleic Acids Res, 35(22): 7417–7428

Childs B G, Baker D J, Kirkland J L, Campisi J, van Deursen J M (2014). Senescence and apoptosis: dueling or complementary cell fates? EMBO Rep, 15(11): 1139–1153

Ciccia A, Elledge S J (2010). The DNA damage response: making it safe to play with knives. Mol Cell, 40(2): 179–204

Cooke M S, Evans M D, Dizdaroglu M, Lunec J (2003). Oxidative DNA damage: mechanisms, mutation, and disease. FASEB J, 17(10): 1195–1214

d'Adda di Fagagna F (2008). Living on a break: cellular senescence as a DNA-damage response. Nat Rev Cancer, 8(7): 512–522

D'Andrea A D, Grompe M (2003). The Fanconi anaemia/BRCA pathway. Nat Rev Cancer, 3(1): 23–34

Das A, Grotsky D A, Neumann M A, Kreienkamp R, Gonzalez-Suarez I, Redwood A B, Kennedy B K, Stewart C L, Gonzalo S (2013). Lamin A Δexon9 mutation leads to telomere and chromatin defects but not genomic instability. Nucleus, 4(5): 410–419

De Bont R, van Larebeke N (2004). Endogenous DNA damage in humans: a review of quantitative data. Mutagenesis, 19(3): 169–185

Dobbin M M, Madabhushi R, Pan L, Chen Y, Kim D, Gao J, Ahanonu B, Pao P C, Qiu Y, Zhao Y, Tsai L H (2013). SIRT1 collaborates with ATM and HDAC1 to maintain genomic stability in neurons. Nat Neurosci, 16(8): 1008–1015

Eriksson M, Brown W T, Gordon L B, Glynn M W, Singer J, Scott L, Erdos M R, Robbins C M, Moses T Y, Berglund P, Dutra A, Pak E, Durkin S, Csoka A B, Boehnke M, Glover T W, Collins F S (2003). Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. Nature, 423(6937): 293–298

Escribano-Díaz C, Orthwein A, Fradet-Turcotte A, Xing M, Young J T, Tkáč J, Cook M A, Rosebrock A P, Munro M, Canny M D, Xu D, Durocher D (2013). A cell cycle-dependent regulatory circuit composed of 53BP1-RIF1 and BRCA1-CtIP controls DNA repair pathway choice. Mol Cell, 49(5): 872–883

Flynn R L, Zou L (2011). ATR: a master conductor of cellular responses to DNA replication stress. Trends Biochem Sci, 36(3): 133–140

Fradet-Turcotte A, Canny M D, Escribano-Díaz C, Orthwein A, Leung C C, Huang H, Landry M C, Kitevski-LeBlanc J, Noordermeer S M, Sicheri F, Durocher D (2013). 53BP1 is a reader of the DNA-damage-induced H2A Lys 15 ubiquitin mark. Nature, 499(7456): 50–54

Friedberg E C, McDaniel L D, Schultz R A (2004). The role of endogenous and exogenous DNA damage and mutagenesis. Curr Opin Genet Dev, 14(1): 5–10

Garinis G A, van der Horst G T, Vijg J, Hoeijmakers J H (2008). DNA damage and ageing: new-age ideas for an age-old problem. Nat Cell Biol, 10(11): 1241–1247

Ghosh S, Liu B, Wang Y, Hao Q, Zhou Z (2015). Lamin A Is an Endogenous SIRT6 Activator and Promotes SIRT6-Mediated DNA Repair. Cell Reports, 13(7): 1396–1406

Gibbs-Seymour I, Markiewicz E, Bekker-Jensen S, Mailand N, Hutchison C J (2015). Lamin A/C-dependent interaction with 53BP1 promotes cellular responses to DNA damage. Aging Cell, 14(2): 162–169

Goldman R D, Shumaker D K, Erdos M R, Eriksson M, Goldman A E, Gordon L B, Gruenbaum Y, Khuon S, Mendez M, Varga R, Collins F S (2004). Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci USA, 101(24): 8963–8968

Gonzalez-Suarez I, Redwood A B, Gonzalo S (2009). Loss of A-type lamins and genomic instability. Cell Cycle, 8(23): 3860–3865

Gonzalez-Suarez I, Redwood A B, Grotsky D A, Neumann M A, Cheng E H, Stewart C L, Dusso A, Gonzalo S (2011). A new pathway that regulates 53BP1 stability implicates cathepsin L and vitamin D in DNA repair. EMBO J, 30(16): 3383–3396

Gonzalo S (2014). DNA damage and lamins. Adv Exp Med Biol, 773: 377–399

Gonzalo S, Kreienkamp R (2015). DNA repair defects and genome instability in Hutchinson-Gilford Progeria Syndrome. Curr Opin Cell Biol, 34: 75–83

Gonzalo S, Kreienkamp R, Askjaer P (2016). Hutchinson-Gilford Progeria Syndrome: A premature aging disease caused by LMNA gene mutations. Ageing Res Rev: S1568-1637(16)30134-9

Gordon L B, Kleinman M E, Miller D T, Neuberg D S, Giobbie-Hurder A, Gerhard-Herman M, Smoot L B, Gordon C M, Cleveland R, Snyder B D, Fligor B, Bishop W R, Statkevich P, Regen A, Sonis A, Riley S, Ploski C, Correia A, Quinn N, Ullrich N J, Nazarian A, Liang M G, Huh S Y, Schwartzman A, Kieran M W (2012). Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci USA, 109(41): 16666–16671

Gordon L B, Massaro J, D'Agostino R B Sr, Campbell S E, Brazier J, Brown W T, Kleinman M E, Kieran M W, and the Progeria Clinical Trials Collaborative (2014). Impact of farnesylation inhibitors on survival in Hutchinson-Gilford progeria syndrome. Circulation, 130 (1): 27–34

Gordon L B, McCarten K M, Giobbie-Hurder A, Machan J T, Campbell S E, Berns S D, Kieran M W (2007). Disease progression in Hutchinson-Gilford progeria syndrome: impact on growth and development. Pediatrics, 120(4): 824–833

Gupta A, Hunt C R, Chakraborty S, Pandita R K, Yordy J, Ramnarain D B, Horikoshi N, Pandita T K (2014). Role of 53BP1 in the regulation of DNA double-strand break repair pathway choice. Radiat Res, 181 (1): 1–8

Haffner M C, De Marzo A M, Meeker A K, Nelson W G, Yegnasubramanian S (2011). Transcription-induced DNA double strand breaks: both oncogenic force and potential therapeutic target? Clin Cancer Res, 17(12): 3858–3864

Helleday T, Eshtad S, Nik-Zainal S (2014). Mechanisms underlying mutational signatures in human cancers. Nat Rev Genet, 15(9): 585–598

Hoeijmakers J H (2009). DNA damage, aging, and cancer. N Engl J Med, 361(15): 1475–1485

Kelman Z (1997). PCNA: structure, functions and interactions. Oncogene, 14(6): 629–640

Kinner A, Wu W, Staudt C, Iliakis G (2008). Gamma-H2AX in recognition and signaling of DNA double-strand breaks in the context of chromatin. Nucleic Acids Res, 36(17): 5678–5694

Kolas N K, Chapman J R, Nakada S, Ylanko J, Chahwan R, Sweeney F

D, Panier S, Mendez M, Wildenhain J, Thomson T M, Pelletier L, Jackson S P, Durocher D (2007). Orchestration of the DNA-damage response by the RNF8 ubiquitin ligase. Science, 318(5856): 1637–1640

Krishnan V, Chow M Z, Wang Z, Zhang L, Liu B, Liu X, Zhou Z (2011). Histone H4 lysine 16 hypoacetylation is associated with defective DNA repair and premature senescence in Zmpste24-deficient mice. Proc Natl Acad Sci USA, 108(30): 12325–12330

Kuo L J, Yang L X (2008). Gamma-H2AX- a novel biomarker for DNA double-strand breaks. In Vivo, 22(3): 305–309

Lavin M F (2008). Ataxia-telangiectasia: from a rare disorder to a paradigm for cell signalling and cancer. Nat Rev Mol Cell Biol, 9 (10): 759–769

Lee J H, Paull T T (2004). Direct activation of the ATM protein kinase by the Mre11/Rad50/Nbs1 complex. Science, 304(5667): 93–96

Lee J H, Paull T T (2005). ATM activation by DNA double-strand breaks through the Mre11-Rad50-Nbs1 complex. Science, 308(5721): 551–554

Lee J H, Paull T T (2007). Activation and regulation of ATM kinase activity in response to DNA double-strand breaks. Oncogene, 26(56): 7741–7748

Li X, Corsa C A, Pan P W, Wu L, Ferguson D, Yu X, Min J, Dou Y (2010). MOF and H4 K16 acetylation play important roles in DNA damage repair by modulating recruitment of DNA damage repair protein Mdc1. Mol Cell Biol, 30(22): 5335–5347

Lin M T, Beal M F (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature, 443(7113): 787–795

Liu B, Ghosh S, Yang X, Zheng H, Liu X, Wang Z, Jin G, Zheng B, Kennedy B K, Suh Y, Kaeberlein M, Tryggvason K, Zhou Z (2012). Resveratrol rescues SIRT1-dependent adult stem cell decline and alleviates progeroid features in laminopathy-based progeria. Cell Metab, 16(6): 738–750

Liu B, Wang J, Chan K M, Tjia W M, Deng W, Guan X, Huang J D, Li K M, Chau P Y, Chen D J, Pei D, Pendas A M, Cadiñanos J, López-Otín C, Tse H F, Hutchison C, Chen J, Cao Y, Cheah K S, Tryggvason K, Zhou Z (2005). Genomic instability in laminopathy-based premature aging. Nat Med, 11(7): 780–785

Liu B, Wang Z, Ghosh S, Zhou Z (2013a). Defective ATM-Kap-1-mediated chromatin remodeling impairs DNA repair and accelerates senescence in progeria mouse model. Aging Cell, 12(2): 316–318

Liu B, Wang Z, Zhang L, Ghosh S, Zheng H, Zhou Z (2013b). Depleting the methyltransferase Suv39h1 improves DNA repair and extends lifespan in a progeria mouse model. Nat Commun, 4: 1868

Liu Y, Rusinol A, Sinensky M, Wang Y, Zou Y (2006). DNA damage responses in progeroid syndromes arise from defective maturation of prelamin A. J Cell Sci, 119(Pt 22): 4644–4649

Liu Y, Wang Y, Rusinol A E, Sinensky M S, Liu J, Shell S M, Zou Y (2008). Involvement of xeroderma pigmentosum group A (XPA) in progeria arising from defective maturation of prelamin A. FASEB J, 22(2): 603–611

Lombard D B, Chua K F, Mostoslavsky R, Franco S, Gostissa M, Alt F W (2005). DNA repair, genome stability, and aging. Cell, 120(4): 497–512

Longhese M P (2008). DNA damage response at functional and dysfunctional telomeres. Genes Dev, 22(2): 125–140

Mahen R, Hattori H, Lee M, Sharma P, Jeyasekharan A D, Venkitaraman A R (2013). A-type lamins maintain the positional stability of DNA damage repair foci in mammalian nuclei. PLoS One, 8(5): e61893

Mailand N, Bekker-Jensen S, Faustrup H, Melander F, Bartek J, Lukas C, Lukas J (2007). RNF8 ubiquitylates histones at DNA double-strand breaks and promotes assembly of repair proteins. Cell, 131(5): 887–900

Malaquin N, Carrier-Leclerc A, Dessureault M, Rodier F (2015). DDR-mediated crosstalk between DNA-damaged cells and their micro-environment. Front Genet, 6: 94

Manju K, Muralikrishna B, Parnaik V K (2006). Expression of disease-causing lamin A mutants impairs the formation of DNA repair foci. J Cell Sci, 119(Pt 13): 2704–2714

Mathew C G (2006). Fanconi anaemia genes and susceptibility to cancer. Oncogene, 25(43): 5875–5884

Mattiroli F, Vissers J H, van Dijk W J, Ikpa P, Citterio E, Vermeulen W, Marteijn J A, Sixma T K (2012). RNF168 ubiquitinates K13-15 on H2A/H2AX to drive DNA damage signaling. Cell, 150(6): 1182–1195

Mazouzi A, Velimezi G, Loizou J I (2014). DNA replication stress: causes, resolution and disease. Exp Cell Res, 329(1): 85–93

McCord R P, Nazario-Toole A, Zhang H, Chines P S, Zhan Y, Erdos M R, Collins F S, Dekker J, Cao K (2013). Correlated alterations in genome organization, histone methylation, and DNA-lamin A/C interactions in Hutchinson-Gilford progeria syndrome. Genome Res, 23(2): 260–269

Merideth M A, Gordon L B, Clauss S, Sachdev V, Smith A C, Perry M B, Brewer C C, Zalewski C, Kim H J, Solomon B, Brooks B P, Gerber L H, Turner M L, Domingo D L, Hart T C, Graf J, Reynolds J C, Gropman A, Yanovski J A, Gerhard-Herman M, Collins F S, Nabel E G, Cannon R O 3rd, Gahl W A, Introne W J (2008). Phenotype and course of Hutchinson-Gilford progeria syndrome. N Engl J Med, 358(6): 592–604

Mirkin E V, Mirkin S M (2007). Replication fork stalling at natural impediments. Microbiol Mol Biol Rev, 71(1): 13–35

Moir R D, Spann T P, Herrmann H, Goldman R D (2000). Disruption of nuclear lamin organization blocks the elongation phase of DNA replication. J Cell Biol, 149(6): 1179–1192

Mostoslavsky R, Chua K F, Lombard D B, Pang W W, Fischer M R, Gellon L, Liu P, Mostoslavsky G, Franco S, Murphy M M, Mills K D, Patel P, Hsu J T, Hong A L, Ford E, Cheng H L, Kennedy C, Nunez N, Bronson R, Frendewey D, Auerbach W, Valenzuela D, Karow M, Hottiger M O, Hursting S, Barrett J C, Guarente L, Mulligan R, Demple B, Yancopoulos G D, Alt F W (2006). Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. Cell, 124(2): 315–329

Murphy M P (2009). How mitochondria produce reactive oxygen species. Biochem J, 417(1): 1–13

Musich P R, Zou Y (2009). Genomic instability and DNA damage responses in progeria arising from defective maturation of prelamin A. Aging (Albany, NY), 1(1): 28–37

Musich P R, Zou Y (2011). DNA-damage accumulation and replicative arrest in Hutchinson-Gilford progeria syndrome. Biochem Soc Trans, 39(6): 1764–1769

Norbury C J, Zhivotovsky B (2004). DNA damage-induced apoptosis. Oncogene, 23(16): 2797–2808

Oberdoerffer P, Michan S, McVay M, Mostoslavsky R, Vann J, Park S K, Hartlerode A, Stegmuller J, Hafner A, Loerch P, Wright S M, Mills K D, Bonni A, Yankner B A, Scully R, Prolla T A, Alt F W,

Sinclair D A (2008). SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. Cell, 135 (5): 907–918

Olcina M M, Foskolou I P, Anbalagan S, Senra J M, Pires I M, Jiang Y, Ryan A J, Hammond E M (2013). Replication stress and chromatin context link ATM activation to a role in DNA replication. Mol Cell, 52(5): 758–766

Oshima J, Martin G M, Hisama F M (1993). Werner Syndrome. GeneReviews(R), eds. Pagon R A, Adam M P, Ardinger H H, Wallace S E, Amemiya A, Bean L J H, Bird T D, Fong C T, Mefford H C, Smith R J H, et al. (University of Washington, Seattle University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved. Seattle (WA)).

Osorio F G, Navarro C L, Cadiñanos J, López-Mejía I C, Quirós P M, Bartoli C, Rivera J, Tazi J, Guzmán G, Varela I, Depetris D, de Carlos F, Cobo J, Andrés V, De Sandre-Giovannoli A, Freije J M, Lévy N, López-Otín C (2011). Splicing-directed therapy in a new mouse model of human accelerated aging. Sci Transl Med, 3(106): 106ra107

Pagano G, Talamanca A A, Castello G, Cordero M D, d'Ischia M, Gadaleta M N, Pallardó F V, Petrović S, Tiano L, Zatterale A (2014). Oxidative stress and mitochondrial dysfunction across broad-ranging pathologies: toward mitochondria-targeted clinical strategies. Oxid Med Cell Longev, 2014: 541230

Panier S, Boulton S J (2014). Double-strand break repair: 53BP1 comes into focus. Nat Rev Mol Cell Biol, 15(1): 7–18

Patel A G, Sarkaria J N, Kaufmann S H (2011). Nonhomologous end joining drives poly(ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells. Proc Natl Acad Sci USA, 108(8): 3406–3411

Paull T T, Rogakou E P, Yamazaki V, Kirchgessner C U, Gellert M, Bonner W M (2000). A critical role for histone H2AX in recruitment of repair factors to nuclear foci after DNA damage. Curr Biol, 10(15): 886–895

Pegoraro G, Kubben N, Wickert U, Göhler H, Hoffmann K, Misteli T (2009). Ageing-related chromatin defects through loss of the NURD complex. Nat Cell Biol, 11(10): 1261–1267

Peinado J R, Quirós P M, Pulido M R, Mariño G, Martínez-Chantar M L, Vázquez-Martínez R, Freije J M P, López-Otín C, Malagón M M (2011). Proteomic profiling of adipose tissue from Zmpste24$^{-/-}$ mice, a model of lipodystrophy and premature aging, reveals major changes in mitochondrial function and vimentin processing. Mol Cell Proteomics, 10(11): M111.008094

Polo S E, Jackson S P (2011). Dynamics of DNA damage response proteins at DNA breaks: a focus on protein modifications. Genes Dev, 25(5): 409–433

Price B D, D'Andrea A D (2013). Chromatin remodeling at DNA double-strand breaks. Cell, 152(6): 1344–1354

Ray Chaudhuri A, Hashimoto Y, Herrador R, Neelsen K J, Fachinetti D, Bermejo R, Cocito A, Costanzo V, Lopes M (2012). Topoisomerase I poisoning results in PARP-mediated replication fork reversal. Nat Struct Mol Biol, 19(4): 417–423

Redwood A B, Gonzalez-Suarez I, Gonzalo S (2011). Regulating the levels of key factors in cell cycle and DNA repair: new pathways revealed by lamins. Cell Cycle, 10(21): 3652–3657

Redwood A B, Perkins S M, Vanderwaal R P, Feng Z, Biehl K J, Gonzalez-Suarez I, Morgado-Palacin L, Shi W, Sage J, Roti-Roti J L, Stewart C L, Zhang J, Gonzalo S (2011). A dual role for A-type lamins in DNA double-strand break repair. Cell Cycle, 10(15): 2549–2560

Richards S A, Muter J, Ritchie P, Lattanzi G, Hutchison C J (2011). The accumulation of un-repairable DNA damage in laminopathy progeria fibroblasts is caused by ROS generation and is prevented by treatment with N-acetyl cysteine. Hum Mol Genet, 20(20): 3997–4004

Rivera-Torres J, Acín-Perez R, Cabezas-Sánchez P, Osorio F G, Gonzalez-Gómez C, Megias D, Cámara C, López-Otín C, Enríquez J A, Luque-García J L, Andrés V (2013). Identification of mitochondrial dysfunction in Hutchinson-Gilford progeria syndrome through use of stable isotope labeling with amino acids in cell culture. J Proteomics, 91: 466–477

Roos W P, Kaina B (2006). DNA damage-induced cell death by apoptosis. Trends Mol Med, 12(9): 440–450

Sahin E, Depinho R A (2010). Linking functional decline of telomeres, mitochondria and stem cells during ageing. Nature, 464(7288): 520–528

Scaffidi P, Misteli T (2005). Reversal of the cellular phenotype in the premature aging disease Hutchinson-Gilford progeria syndrome. Nat Med, 11(4): 440–445

Schmitt E, Paquet C, Beauchemin M, Bertrand R (2007). DNA-damage response network at the crossroads of cell-cycle checkpoints, cellular senescence and apoptosis. J Zhejiang Univ Sci B, 8(6): 377–397

Schreiber K H, Kennedy B K (2013). When lamins go bad: nuclear structure and disease. Cell, 152(6): 1365–1375

Shiloh Y, Ziv Y (2013). The ATM protein kinase: regulating the cellular response to genotoxic stress, and more. Nat Rev Mol Cell Biol, 14(4): 197–210

Shrivastav M, De Haro L P, Nickoloff J A (2008). Regulation of DNA double-strand break repair pathway choice. Cell Res, 18(1): 134–147

Shumaker D K, Dechat T, Kohlmaier A, Adam S A, Bozovsky M R, Erdos M R, Eriksson M, Goldman A E, Khuon S, Collins F S, Jenuwein T, Goldman R D (2006). Mutant nuclear lamin A leads to progressive alterations of epigenetic control in premature aging. Proc Natl Acad Sci USA, 103(23): 8703–8708

Singh M, Hunt C R, Pandita R K, Kumar R, Yang C R, Horikoshi N, Bachoo R, Serag S, Story M D, Shay J W, Powell S N, Gupta A, Jeffery J, Pandita S, Chen B P, Deckbar D, Löbrich M, Yang Q, Khanna K K, Worman H J, Pandita T K (2013). Lamin A/C depletion enhances DNA damage-induced stalled replication fork arrest. Mol Cell Biol, 33(6): 1210–1222

Sirbu B M, Cortez D (2013). DNA damage response: three levels of DNA repair regulation. Cold Spring Harb Perspect Biol, 5(8): a012724

Stewart G S, Wang B, Bignell C R, Taylor A M, Elledge S J (2003). MDC1 is a mediator of the mammalian DNA damage checkpoint. Nature, 421(6926): 961–966

Stiff T, O'Driscoll M, Rief N, Iwabuchi K, Löbrich M, Jeggo P A (2004). ATM and DNA-PK function redundantly to phosphorylate H2AX after exposure to ionizing radiation. Cancer Res, 64(7): 2390–2396

Sun Y, Jiang X, Chen S, Fernandes N, Price B D (2005). A role for the Tip60 histone acetyltransferase in the acetylation and activation of ATM. Proc Natl Acad Sci USA, 102(37): 13182–13187

Sun Y, Jiang X, Xu Y, Ayrapetov M K, Moreau L A, Whetstine J R,

Price B D (2009). Histone H3 methylation links DNA damage detection to activation of the tumour suppressor Tip60. Nat Cell Biol, 11(11): 1376–1382

Tang H, Hilton B, Musich P R, Fang D Z, Zou Y (2012). Replication factor C1, the large subunit of replication factor C, is proteolytically truncated in Hutchinson-Gilford progeria syndrome. Aging Cell, 11 (2): 363–365

Tubbs A T, Sleckman B P (2014). ATM deficiency: revealing the pathways to cancer. Cell Cycle, 13(19): 2992

Varga R, Eriksson M, Erdos M R, Olive M, Harten I, Kolodgie F, Capell B C, Cheng J, Faddah D, Perkins S, Avallone H, San H, Qu X, Ganesh S, Gordon L B, Virmani R, Wight T N, Nabel E G, Collins F S (2006). Progressive vascular smooth muscle cell defects in a mouse model of Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci USA, 103(9): 3250–3255

Verstraeten V L, Peckham L A, Olive M, Capell B C, Collins F S, Nabel E G, Young S G, Fong L G, Lammerding J (2011). Protein farnesylation inhibitors cause donut-shaped cell nuclei attributable to a centrosome separation defect. Proc Natl Acad Sci USA, 108(12): 4997–5002

Viteri G, Chung Y W, Stadtman E R (2010). Effect of progerin on the accumulation of oxidized proteins in fibroblasts from Hutchinson Gilford progeria patients. Mech Ageing Dev, 131(1): 2–8

Ward I M, Chen J (2001). Histone H2AX is phosphorylated in an ATR-dependent manner in response to replicational stress. J Biol Chem, 276(51): 47759–47762

Xiong Z M, Choi J Y, Wang K, Zhang H, Tariq Z, Wu D, Ko E, LaDana C, Sesaki H, Cao K (2015). Methylene blue alleviates nuclear and mitochondrial abnormalities in progeria. Aging Cell

Xiong Z M, Choi J Y, Wang K, Zhang H, Tariq Z, Wu D, Ko E, LaDana C, Sesaki H, Cao K (2016). Methylene blue alleviates nuclear and mitochondrial abnormalities in progeria. Aging Cell, 15(2): 279–290

Yang S H, Meta M, Qiao X, Frost D, Bauch J, Coffinier C, Majumdar S, Bergo M O, Young S G, Fong L G (2006). A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson-Gilford progeria syndrome mutation. J Clin Invest, 116(8): 2115–2121

Yang S H, Qiao X, Fong L G, Young S G (2008). Treatment with a farnesyltransferase inhibitor improves survival in mice with a Hutchinson-Gilford progeria syndrome mutation. Biochim Biophys Acta, 1781(1-2): 36–39

Zhang H, Kieckhaefer J E, Cao K (2013). Mouse models of laminopathies. Aging Cell, 12(1): 2–10

Zhang H, Xiong Z M, Cao K (2014). Mechanisms controlling the smooth muscle cell death in progeria via down-regulation of poly (ADP-ribose) polymerase 1. Proc Natl Acad Sci USA, 111(22): E2261–E2270

Zhang W, Li J, Suzuki K, Qu J, Wang P, Zhou J, Liu X, Ren R, Xu X, Ocampo A, Yuan T, Yang J, Li Y, Shi L, Guan D, Pan H, Duan S, Ding Z, Li M, Yi F, Bai R, Wang Y, Chen C, Yang F, Li X, Wang Z, Aizawa E, Goebl A, Soligalla R D, Reddy P, Esteban C R, Tang F, Liu G H, Belmonte J C (2015). Aging stem cells. A Werner syndrome stem cell model unveils heterochromatin alterations as a driver of human aging. Science, 348(6239): 1160–1163

Zhou B B, Elledge S J (2000). The DNA damage response: putting checkpoints in perspective. Nature, 408(6811): 433–439

Zimmermann M, Lottersberger F, Buonomo S B, Sfeir A, de Lange T (2013). 53BP1 regulates DSB repair using Rif1 to control 5′ end resection. Science, 339(6120): 700–704