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Review

Lamin A involvement in ageing processes

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ABSTRACT

Lamin A, a main constituent of the nuclear lamina, is the major splicing product of the *LMNA* gene, which also encodes lamin C, lamin A delta 10 and lamin C2. Involvement of lamin A in the ageing process became clear after the discovery that a group of progeroid syndromes, currently referred to as progeroid laminopathies, are caused by mutations in *LMNA* gene. Progeroid laminopathies include Hutchinson-Gilford Progeria, Mandibuloacral Dysplasia, Atypical Progeria and atypical-Werner syndrome, disabling and life-threatening diseases with accelerated ageing, bone resorption, lipodystrophy, skin abnormalities and cardiovascular disorders. Defects in lamin A post-translational maturation occur in progeroid syndromes and accumulated prelamin A affects ageing-related processes, such as mTOR signaling, epigenetic modifications, stress response, inflammation, microRNA activation and mechanosignaling. In this review, we briefly describe the role of these pathways in physiological ageing and go in deep into lamin A-dependent mechanisms that accelerate the ageing process. Finally, we propose that lamin A acts as a sensor of cell intrinsic and environmental stress through transient prelamin A accumulation, which triggers stress response mechanisms. Exacerbation of lamin A sensor activity due to stably elevated prelamin A levels contributes to the onset of a permanent stress response condition, which triggers accelerated ageing.

1. Introduction

The *LMNA* gene encodes lamin A, lamin C and minor products lamin C2 and lamin A delta 10, which are produced by alternative splicing. Lamin A and lamin C are main constituents of the nuclear lamina underneath the inner nuclear membrane (Camozzi et al., 2014; Turgay et al., 2017). They are expressed in almost all differentiated tissues, although lamin A is downregulated in brain (Jung et al., 2012). Lamin A and its nuclear envelope partners, such as emerin, B-type lamins, lamin B receptor (LBR), Barrier to Autointegration Factor (BAF), the nesprins, SUN1 and SUN2, feature important structural functions in nuclear organization and/or serve as regulators of diverse nuclear processes, while LBR and the prelamin A endoprotease ZMPSTE24 (Zinc Metallopeptidase STE24) have enzymatic properties (Camozzi et al., 2014; Cenni et al., 2018; Maraldi et al., 2011; Meinke et al., 2014; Wang et al., 2016).

Mutations in nuclear lamina/nuclear envelope proteins cause rare genetic diseases collectively referred to as laminopathies (Camozzi et al., 2014; Cenni et al., 2018). More than 400 mutations in *LMNA* have been hitherto identified as causative of diseases, from Emery-Dreifuss Muscular Dystrophy and Dilated Cardiomyopathy with Conduction defects, up to Familial Partial Lipodystrophy of the Dunnigan-Type (FPLD2) and syndromic laminopathies (Cenni et al., 2018). In this review, we will linger on systemic laminopathies featuring accelerated ageing, referred to as progeroid laminopathies, and will focus on ageing-related cellular processes implicated in the pathomechanisms of these diseases. Progeroid laminopathies include Hutchinson-Gilford Progeria Syndrome (HGPS), Atypical Progeria Syndrome (APS), type A Mandibuloacral Dysplasia (MADA), type B Mandibuloacral Dysplasia (MADB), and Atypical-Werner's Syndrome (A-WS) (Cenni et al., 2018;

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Doubaj et al., 2012). Except for MADB, which is due to mutations of the prelamin A endoprotease ZMPSTE24, progeroid laminopathies are caused by *LMNA* gene mutations, which are dominant in the case of HGPS, A-WS and APS and recessive in most cases of MADA (Cenni et al., 2018; Gargiuli et al., 2018). Both compound heterozygous mutations and homozygous mutations in *ZMPSTE24* gene, causing prelamin A accumulation, have been associated with MADB (Cenni et al., 2018). However, ZMPSTE24 functionality is in part preserved in this disease, while complete loss of enzyme function, with accumulation of prelamin A in the absence of mature lamin A, causes a severe developmental disease with perinatal death called Restrictive dermopathy (RD) (Cenni et al., 2018; Columbaro et al., 2010; Navarro et al., 2004).

From a clinical point of view, progeroid laminopathies feature short stature, thinning and graying of hair, a "bird-like" facial appearance with beaked nose, focal osteolysis, skin atrophy, lipodystrophy, along with other age-related disorders such as osteoporosis, atherosclerosis as well as cardiac and cardiovascular defects. In progeroid laminopathies, ageing-related symptoms progressively worsen and may become life-threatening due to cardiovascular involvement (Cenni et al., 2018; Hamczyk et al., 2018; Olive et al., 2010). The age at onset, as well as the rate of appearance and severity of clinical symptoms varies depending on the syndrome and in some instances among individuals. Symptoms indeed appear a few months after birth in HGPS, in the first years of life in APS and MADB, or at the end of the first decade in MADA and A-WS (Cenni et al., 2018).

Starting from the discovery of lamin A involvement in MADA and HGPS, more than sixteen years of research on progeroid laminopathies have provided diverse and sometimes unexpected data on lamin A involvement in ageing-related cellular pathways (Cenni et al., 2018). We believe that it is now possible to recapitulate available data and envisage a unique role for lamin A of cellular sensor in each of those pathways.

2. Prelamin A processing and "progeroid lamins"

A main molecular determinant of progeroid laminopathies is partially processed prelamin A. Prelamin A is a 664 amino acid protein, which undergoes four post-translational modifications leading to production of 647 amino acid-long mature lamin A. Processing occurs at the nuclear membrane starting with farnesylation of the cysteine residue in the C-terminal -CSIM sequence. Then, a first proteolytic cut removes the last three residues, exposing the cysteine to carboxymethylation driven by ICMT (IsoprenylCysteine MethylTransferase); finally, a second cleavage, performed by ZMPSTE24 at leucine 647, removes the last 15 amino acids and yields the mature protein (Barrowman et al., 2012; Lattanzi, 2011; Maraldi et al., 2011). Prelamin A is almost undetectable under physiological conditions due to very fast maturation (Lattanzi, 2011). However, protein processing is slowed-down upon myoblast differentiation, stress stimuli or in senescent cells. Thus, prelamin A is directly involved in myonuclear positioning and stress response, while moderate accumulation of prelamin A has been shown to reduce invasiveness of cancer cells (Angori et al., 2017;Cenni et al., 2019 de la Rosa et al., 2013; Lattanzi et al., 2014; Mattioli et al., 2019; Mattioli et al., 2011). Moreover, prelamin A increase in centenarian cells favors recruitment of DNA damage response (DDR) machinery and DNA repair (Lattanzi et al., 2014). This suggests that pathogenetic effects of prelamin A occur only beyond a threshold level of protein accumulation, while low amounts are well tolerated and under certain conditions even beneficial for the cell. Along this line, the pathogenetic effects become evident in laminopathic cells beyond a certain threshold of protein accumulation and worsen with increasing levels of prelamin A (Columbaro et al., 2005; Filesi et al., 2005; Goldman et al., 2004).

In HGPS, the *n*.1824C > T mutation in *LMNA* gene is responsible for a silent mutation (*p*.G608 G), which introduces a cryptic splice site in the primary transcript causing an in-frame deletion of fifty amino acids in prelamin A. The truncated protein undergoes farnesylation, but removal of the farnesylated C-terminal residue is abrogated and a farnesylated, highly stable prelamin A form, called progerin is produced (Eriksson et al., 2003; Harhouri et al., 2016; Pellegrini et al., 2015). In the case of MADB, partial loss of function of ZMPSTE24 causes accumulation of wild-type prelamin A to toxic levels (Agarwal et al., 2003). In MADA, A-WS and APS, prelamin A accumulation has been also reported (Camozzi et al., 2012; Capanni et al., 2012; Filesi et al., 2005). Although the reason why prelamin A is increased in those syndromes is still unclear, it has been reported that diverse prelamin A post-translational processing products coexist in cells from MADA, as also reported for MADB (Camozzi et al., 2012; Cenni et al., 2014; Cenni et al., 2018). Of note, in most progeroid laminopathies, prelamin A carries a missense mutation or a deletion, which could directly affect intermolecular interactions and/or protein stability (Cenni et al., 2018; Spear et al., 2018). However, given the striking similarity between the phenotype of MADB and HGPS (featuring wild-type and mutated prelamin A accumulation, respectively), as well as between the corresponding mouse models, the main pathogenetic role of prelamin A accumulation appears obvious (Cenni et al., 2018; Osorio et al., 2012).

In this review we refer to the prelamin A forms involved in progeroid syndromes as "progeroid lamins"Table 1, i.e. those lamin A forms, that, when accumulated to toxic levels, elicit cellular and organismal ageing. Accumulation of progeroid lamins promptly impacts on

Table 1
Progeroid lamins. Progeroid lamins are lamin A forms, including wild-type prelamin A, which become toxic to cells and induce organism ageing beyond a threshold level of accumulation in cells and organism. Type of progeroid lamin, presence of Cysteine farnesylation in the C-terminal CSIM box of prelamin A, gene and type of mutation, behavior of mature lamin A in the corresponding disease, behavior of lamin C in the corresponding disease cells, name of the disease(s), type of inheritance are indicated. For further details and bibliography, see chapter 2.

PROGEROID LAMIN	Farnesylation at the CSIM box	Mutation	Mature lamin A	Lamin C	Disease	Inheritance
Wild-type prelamin A	Farnesylated	No mutation in *LMNA*, mutation in *ZMPSTE24*	Wild-type, reduced	Wild-type	MADB	compound heterozygous
Mutated prelamin A	Farnesylated and non-farnesylated	Missense mutation in the C-terminus of lamin A/C	Mutated, normal amount	Mutated, normal amount	MADA	homozygous or compound heterozygous
Progerin (prelamin A delta 50)	Farnesylated	50 amino acid deletion in the C-terminus of prelamin A	Wild-type, reduced	Wild-type, reduced	HGPS	heterozygous
Prelamin A delta 35 or delta 90	Farnesylated	35 or 90 amino acid deletion in prelamin A C-terminus	Wild-type, reduced	Wild-type, normal amount?	HGPS	heterozygous
Mutated prelamin A	?	Missense mutation in the N-terminus of lamin A/C	Mutated, normal amount	Mutated, normal amount	A-WS APS	heterozygous

nuclear phenotype. Nuclei become misshapen, presenting blebs, folds or gross irregularities in shape and feature diverse patterns of chromatin disorganization (Camozzi et al., 2012; Columbaro et al., 2005; Lombardi et al., 2007; Pellegrini et al., 2015). Increased nuclear stiffness and altered mechanical stress response are also associated with progeroid lamin expression (Cho et al., 2018; Ho et al., 2013; Osmanagic-Myers et al., 2015; Vidak et al., 2018). Nuclear defects can be related to prelamin A or progerin effect on nuclear envelope proteins, mainly SUN1, a main component of the LINC complex, emerin and BAF, a key mediator of lamin-DNA interaction targeted to the nuclear envelope by prelamin A (Capanni et al., 2010; Capanni et al., 2012). Further, by affecting recruitment of transcription factors, epigenetic regulators and DNA repair enzymes, progeroid lamins may alter gene expression and repair of damaged DNA (Capanni et al., 2005; Cenni et al., 2014; Kubben et al., 2016; Mattioli et al., 2018; Mattioli et al., 2019).

Overall, altered nuclear dynamics elicited by progeroid lamins appears to be the result of an unwanted/unscheduled signal and impacts on several cellular processes. The following paragraphs focus on each of these processes and suggest a common role of lamin A as sensor of cellular and environmental stress, which is exacerbated by unscheduled accumulation of prelamin A forms leading to accelerated ageing (Burtner and Kennedy, 2010; Kubben and Misteli, 2017).

3. mTOR signaling and progeroid lamins

3.1. mTOR signaling in ageing processes

Signaling through mTOR (mechanistic target of rapamycin) has been extensively studied for its involvement in ageing processes and it is generally accepted that low mTOR activity favors lifespan extension (Lee et al., 2020).

Among ageing-related processes, autophagy, which is triggered by mTOR inhibition, is aimed at degradation of defective molecules and organelles that accumulate in cells during stress, starvation and senescence. Multiple studies demonstrated that a poor autophagic activity is a hallmark of ageing-related disorders including cardiovascular diseases, cancer, arthritis, cataract, osteoporosis, type 2 diabetes, hypertension and neurodegenerative disorders (such as Parkinson's or Alzheimer's disease), while treatment with rapamycin, possibly the best-known mTOR inhibitor and autophagy-inducing drug, significantly extended life-span in mammals (Bitto et al., 2016; Chiarini et al., 2019).

Moreover, mTOR, in particular the mTORC1 complex, is also engaged in anabolic processes such as cell growth and proliferation in response to nutrient sensing, another pathway implicated in lifespan (Evangelisti et al., 2016) Lee et al., 2019). In fact, both circulating nutrient sensing factors, such as the insulin-like growth factor 1 (IGF-1), insulin and growth hormone, and amino acid availability at the lysosome may activate mTOR through the PI3K/AKT signaling pathway (Johnson, 2018). Even in this context, reduced mTOR activity, either determined by caloric restriction or by low circulating IGF-1 levels, has been linked to lifespan and health-span extension (Bucci et al., 2013; Budel and Djabali, 2017; Johnson, 2018; Kubben and Misteli, 2017; Vitale et al., 2019).

mTOR activity can be inhibited by diverse types of stress conditions (Heberle et al., 2015). However, mTOR can be also activated by stress stimuli and drive an adaptive response that triggers anti-oxidant transcription factors such as nuclear factor erythroid 2–related factor 2 (Nrf2) or p53 (Heberle et al., 2015). Short-term stress typically increases mTORC1 activity, while prolonged stress conditions have an inhibitory effect (Heberle et al., 2015). However, the final outcome of stress stimuli targeting mTOR components is dependent on a plethora of effectors and feedback mechanisms that may also vary in different cell types (Aramburu et al., 2014). In this complex scenario, prelamin A modulation appears to play a role.

mTOR activity is influenced by lamin A and prelamin A levels, as indicated by several studies (Barcena et al., 2019; Cenni et al., 2014; Evangelisti et al., 2015; Evangelisti et al., 2016; Ibrahim et al., 2013; Infante et al., 2014; Liao et al., 2016). However, prelamin A has been shown to trigger AKT1 activity, which is expected to activate mTOR, while mTOR is either inhibited (Evangelisti et al., 2016) or slightly affected (Ibrahim et al., 2013) in the presence of prelamin A forms. Of some help, are the intriguing results reported by Ibrahim et al., who showed that low prelamin A levels activate AKT, while prelamin A accumulation to pathogenetic levels, as occurs in *Zmpste24* null mice, inhibits AKT activity (Ibrahim et al., 2013). Consistent with the latter observation, we found that transient accumulation of L647R-mutated farnesylated prelamin A in cells activates AKT (Evangelisti et al., 2015), while accumulation of progerin in progeria cells inhibits mTOR and activates autophagy (Evangelisti et al., 2016), as also demonstrated in very important studies (Barcena et al., 2019; Kreienkamp et al., 2018).

A systematic evaluation of prelamin A role in mTOR regulation upon stress has been only performed under starvation-induced stress conditions. In that context, prelamin A has been shown to inhibit the mTORC1 pathway, an effect not determined by the sole accumulation of prelamin A (Infante et al., 2014). This very interesting observation suggests that prelamin A effects on mTOR are a response to stress conditions and we can speculate that prolonged stress stimuli might reduce mTOR activity at least in part through prelamin A accumulation (Chen et al., 2020; Lattanzi et al., 2014). This hypothesis is also suggested by studies performed in progeroid laminopathies.

3.2. mTOR signaling and progeroid lamins

Autophagic signaling has been investigated in progeroid laminopathies and several dysregulated molecules have been identified in the pathway. In *Zmpste24-/-* mice, which accumulate toxic levels of prelamin A and have a dramatically shortened lifespan, autophagy was activated as AMPK activity was upregulated leading to reduced mTOR and S6 kinase phosphorylation in liver and skeletal muscle (Ibrahim et al., 2013; Marino et al., 2008). Reduced mTOR activity was also observed in HGPS fibroblasts (Evangelisti et al., 2016; Ibrahim et al., 2013). More recently, based on a study performed in $Lmna^{G609G/G609G}$ progeroid mice, which feature highly accelerated ageing, activation of autophagy has been proposed as a mechanism to recycle nutrients in the attempt to counteract weight loss and cachexia (Kreienkamp et al., 2019). In line with the latter hypothesis, when progeroid mice were subjected to high fat diet, LC3 II levels were reduced, suggesting downregulation of autophagy (Kreienkamp et al., 2019). Dysregulation of autophagy has been also observed in FPLD2 adipocytes, which also feature accumulation of prelamin A (Pellegrini et al., 2019). Since impaired autophagy affected adipocyte determination and differentiation in FPLD2 cells, we cannot rule out that altered autophagic activity could specifically impact on adipose tissue turnover even in progeroid laminopathies (Pellegrini et al., 2019).

In the mTOR nutrient sensing pathway, IGF-1 was investigated in preclinical models of progeria. Despite the recognized role of IGF-1 downregulation in lifespan extension, IGF-1 levels were decreased in $Zmpste24^{-/-}$ mice and, most importantly, recombinant IGF-1 treatment restored the growth hormoneIGF-1 axis and prolonged survival of those progeroid mice (Marino and Lopez-Otin, 2008; Marino et al., 2010). Further, a significant increment in respiration rate and energy expenditure was recently reported in $Lmna^{G609G/G609G}$ mice (Barcena et al., 2019; Kreienkamp et al., 2018). Under basal conditions, p70S6K and AKT-Serine473 were hypo-phosphorylated, while AMPK was activated, a condition mimicking extreme dietary restriction, so that dietary restriction (methionine deprivation) did not significantly change their activation state nor increased energy expenditure (Barcena et al., 2019). Conversely, and in agreement with the possibility that excess energy expenditure might contribute to the short lifespan, a paper by the Gonzalo group showed that $Lmna^{G609G/G609G}$ mice subjected to high-fat diet have an impressive increase in life-span, yet they

ultimately develop a severe ageing phenotype (Kreienkamp et al., 2018). Considering that generalized fat loss is probably the most consistent feature both in animal models of progeria and A-WS and HGPS patients, we anticipate that investigating nutrient sensing and energy expenditure pathways with focus on mTOR regulation will provide new and most relevant insights into disease pathogenesis. As a whole, we can observe that exacerbation of mTOR-related signaling in HGPS mouse models and HGPS fibroblasts, leading to excess autophagic activity and energy expenditure appears to take part in HGPS pathogenesis. Whether reduction of IGF-1 and mTOR activity, hyperactivation of autophagy and increased energy expenditure are an attempt to counteract the ageing process or they are an aberrant response to stress or metabolic signals that ultimately causes premature ageing is discussed below.

3.3. Targeting mTOR/autophagy axis as a therapeutic tool in progeroid laminopathies

We have demonstrated that phosphorylation at Serine 404 of lamin A and prelamin A by AKT increases the susceptibility of these molecules to lysosomal degradation (Bertacchini et al., 2013; Cenni et al., 2008). However, Serine 404 phosphorylation mostly triggers degradation of nonfarnesylated prelamin A (Bertacchini et al., 2013). Thus, despite mTOR inhibition, autophagic degradation of progeroid lamins, which are farnesylated, either does not occur as in HGPS or it is not sufficient to lower protein amount to non-toxic levels (Cenni et al., 2014 and 2018). Hence, activators of autophagy, including rapamycin, have been explored in progeroid cells for their ability to trigger progerin or prelamin A degradation (Akinci et al., 2017; Cao et al., 2011; Cenni et al., 2011; Cenni et al., 2014; Evangelisti et al., 2016; Gabriel et al., 2016; Graziotto et al., 2012; Pellegrini et al., 2015). Rapamycin was also used in combination with All-Trans-Retinoic Acid (ATRA) in order to counteract progerin accumulation both at the transcriptional level (by ATRA-induced downregulation of *LMNA* transcripts) and through protein degradation (Pellegrini et al., 2015). This approach improved the phenotype of HGPS cells (Pellegrini et al., 2015). Besides rapamycin, other direct or indirect activators of autophagy have been tested in experimental models of progeria. MG132 treatment of HGPS fibroblasts increased progerin clearance in part by induction of autophagy (Harhouri et al., 2017). Sulforaphane, a natural antioxidant, stimulated autophagy and enhanced progerin degradation in HGPS fibroblasts, an effect also observed under intermittent treatment in combination with FTIs (Gabriel et al., 2017; Lu and Djabali, 2018). Treatment of progerin accumulating cells with metformin, a known anti-diabetic drug able to induce autophagy, rescued nuclear phenotype, decreased ROS amount, upregulated SOD2 antioxidant enzyme, delayed cellular senescence and premature osteogenic differentiation (Egesipe et al., 2016; Park and Shin, 2017). Although metformin-mediated reduction of progerin seems to be a transcriptional effect, it is worth to deepen the study of this safe and easily available drug as a strategy to treat progeroid laminopathies, even more since multiple studies support a role for metformin supplementation in lifespan increase in *C. elegans* and mice (Anisimov et al., 2008). Resveratrol was also able to induce autophagy in progeroid cells (Park et al., 2016). However, there are conflicting evidences about the use of this drug in laminopathic conditions (Liu et al., 2012; Strandgren et al., 2015). Thus, published data point to autophagy-activating drugs as tools to counteract progeroid phenotype, yet further experimental confirmation is needed (Lee et al., 2020). An ongoing clinical trial is testing treatment of HGPS patients with everolimus (font: https://clinicaltrials.gov), which could provide further and more relevant cues.

4. Epigenetic defects in progeroid laminopathies

4.1. Epigenetics in normal ageing

Epigenetic patterns are largely remodeled during physiological ageing (Benayoun et al., 2015). At a global level, a large-scale loss of heterochromatin is observed in ageing cells (Villeponteau, 1997), coupled with the formation of senescence-associated heterochromatin foci (SAHFs) (Narita et al., 2003). Reproducible alterations in histone modification patterns have been described, including a decrease in histone methylation marks associated with inactive chromatin (like H3K9me3 and H3K27me3) and an increase in those associated with active chromatin (like H3K4me3) (see Benayoun et al., for a review (Benayoun et al., 2015)). A global decrease in DNA methylation levels concurs to age-associated heterochromatin loss, ultimately resulting in deregulated gene expression and increased transcription of transposable elements (Phalke et al., 2009). A recent paper shows that activation of LINE-1 retrotransposons causes a type I interferon-driven inflammatory response in senescent cells (De Cecco et al., 2019).

The regulation of histone acetylation in ageing is less characterized and more context-dependent, as differences between species, tissue and target lysine residues have been reported (Peleg et al., 2016). In mammals, H3K56ac and H4K16ac levels decrease during cell senescence, possibly contributing to altered gene expression, response to DNA damage and genomic instability, including telomere damage (O'Sullivan et al., 2010). Finally, locus-specific changes in histone modifications and DNA methylation have been described. Age-associated changes in DNA methylation of specific CpG sites have been described in different human and mouse tissues, leading to the implementation of epigenetic clocks that, on the basis of DNA methylation values, predict the age of an individual (Horvath and Raj, 2018). Importantly, epigenetic clocks are associated with lifespan and healthspan and, more in general, tend to be sensitive to age-related conditions: accelerated age estimations have been described for example in Alzheimer's disease, Parkinson's disease, Down syndrome and obesity, while models of healthy ageing like centenarians and their offspring display younger epigenetic ages than expected (Horvath et al., 2015).

Remodeling of chromosome domains is also a feature of senescent cells. In fact, senescent cells are characterized by a relative loss of long-range and gain of short-range interactions within chromosomes (Criscione et al., 2016). Involvement of lamins in ageing-associated epigenetic regulation may occur through direct interaction with chromatin at specific DNA sequences called lamina-associated domains or LADs (Camozzi 2014; Forsberg et al., 2019). During oncogene-induced cellular senescence, remodeling of LADs elicits an unexpected recruitment of derepressed sequences to the nuclear lamina (Briand and Collas, 2018; Lenain et al., 2017).

Further, lamins contribute to senescence-associated epigenetic changes through epigenetic enzyme functional interactions. (Kanfi et al., 2012). Under physiological conditions and in young cells, lamin A/C binds sirtuins involved in ageing-related mechanisms. Lamin A interacts with SIRT1 to enhance its deacetylase activity, promotes SIRT6 function during DNA repair and recruits histone deacetylase 2 (HDAC2) (Ghosh et al., 2015; Liu et al., 2012; Mattioli et al., 2018 and 2019). Importantly, lamin A interaction with SIRT1, HDAC2 and SIRT6 is reduced upon prelamin A or progerin accumulation (Ghosh et al., 2013; Mattioli et al., 2019; Ghosh et al., 2015). We recently demonstrated that reduced lamin A-HDAC2 interaction during transient stress response is due to prelamin A accumulation and contributes to transient decrease of HDAC2 activity and increase in histone acetylation, which allow repair mechanisms (Mattioli et al., 2019). In the case of SIRT1 and SIRT6, analogous modulation of lamin A interaction through transient prelamin A accumulation under stress conditions appears conceivable. Thus, lamin-related epigenetic mechanisms take advantage of the unique property of lamin A of being transiently kept in its immature form under certain cellular or environmental conditions, including stress stimuli. Due to different affinity of prelamin A versus mature lamin A for epigenetic enzymes, prelamin A post-translational processing provides a tool to modulate chromatin epigenetic modifications. However, the physiological role of lamins as sensors is altered by persistent accumulation of progeroid lamins, which, at the

epigenetic level, impairs histone driven chromatin dynamics, as detailed below.

4.2. Epigenetics in progeroid laminopathies

Some marked similarities exist between the epigenetic changes that occur in physiological ageing and those described in progeroid laminopathies. Decrease in H3K9me3 levels have been described in HGPS and MADA cells (Columbaro et al., 2005; Filesi et al., 2005). Altered regulation of the heterochromatin protein HP1 has been also documented and other heterochromatin marks have been implicated in HGPS cellular phenotype, including H3K27me3 and H4K20me3 (Filesi et al., 2005; McCord et al., 2013; Scaffidi and Misteli, 2006; Shumaker et al., 2006). Moreover, hypoacetylation of H4K16 was reported in a mouse model of progeria deficient for the lamin A processing enzyme Zmpste24, while H4K16ac was increased in HGPS cells and H3K9ac was increased in MADA cells (Cenni et al., 2014; Krishnan et al., 2011; Mattioli et al., 2018). Altered DNA methylation levels at specific CpG sites were further observed in immortalized B-cells from HGPS patients (Heyn et al., 2013). Interestingly, the same cells were older than expected according to the epigenetic clock (Horvath, 2013; Horvath et al., 2018; Wang and Guo, 2015). In the remodeling of HGPS cell epigenetic landscape also LADs have been involved (Shah et al., 2013).

Epigenetic changes occurring in progeroid laminopathies involve HDACs, including sirtuins. In HGPS cells, progerin impairs lamin A/C interaction with SIRT1 and SIRT6, affecting both their chromatin localization and their deacetylase function (Ghosh et al., 2015; Liu et al., 2012). In MADA fibroblasts, SIRT1 anchorage to the nuclear matrix is impaired, while reduction of prelamin A levels by rapamycin treatment rescues enzyme recruitment (Cenni et al., 2014). Lamin A/C is also a component of nucleosome remodeling deacetylase complex (NURD), which is formed by HDAC1, RBBP4 and RBBP7, and reduction of NURD functionality has been observed in HGPS cells (Pegoraro et al., 2009).

We have demonstrated a dynamic interaction between lamin A/C and HDAC2, able to modulate HDAC2 activity in human fibroblasts (Mattioli et al., 2018). A dominant negative effect of progerin on HDAC2 recruitment by lamin A/C, has been observed in HGPS cells, with downstream effects on acetylation of HDAC2 substrates H3K9 and H4K16 (Mattioli et al., 2018). Reduced lamin A/C-HDAC2 affinity has been also shown in other progeroid laminopathies, as APS and MADA (Mattioli et al., 2018). HDAC defects are linked to alter transcriptional activity in progeroid laminopathies, as demonstrated for p21 and Forkhead box class O-3a (FOXO3a). *CDKN1A* gene, encoding p21, a main determinant of cellular senescence, is upregulated upon release of lamin A/C-HDAC2 interaction in HGPS cells (Mattioli et al., 2018). Accumulation of prelamin A in *Zmpste*24 knockout bone marrow stromal cells reduces SIRT1 functionality thus causing hyperacetylation and activation of FOXO3a, a transcription factor involved in stress response and longevity (Auguste et al., 2018; Liu et al., 2012; Morris et al., 2015; Wang et al., 2017). Since both lamin A and FOXO3a are recruited to the p21 promoter, dysregulation of HDAC2 due to progerin accumulation might induce p21-dependent geroconversion of cells through a FOXO3a dependent mechanism. Of particular interest for HGPS pathogenesis, it has been demonstrated that HDAC2 activity is crucial for endothelial function as the enzyme forms a complex with retinoic acid receptor at the p21 promoter to inhibit p21 expression in those cells (Zheng et al., 2011). This mechanism appears to have a protective action and prevent vascular diseases, the main cause of death in HGPS (Olive et al., 2010; Pandey et al., 2014). However, epigenetic effects of progerin or prelamin A accumulation contribute to altered stress response, possibly the main cellular event dysregulated by progeroid lamins, as discussed in the following paragraphs.

5. Progeroid lamins and stress

5.1. Stress response in normal ageing

Oxidative stress is a state of imbalance between free radical production and their degradation by antioxidant systems, with consequent accumulation of reactive oxygen species (ROS) (Liguori et al., 2018). The free-radical theory of ageing claims that failure to regulate intracellular ROS levels is the major determinant of lifespan (Liguori et al., 2018). The most relevant effect of oxidative stress is DNA damage, which can be either efficiently repaired or accumulated, in the latter case leading to a cellular response aimed at limiting mutational events through cell geroconversion (Leontieva and Blagosklonny, 2014; Mattioli et al., 2018). Moreover, replicative stress can be induced by telomere shortening: this mechanism, which avoids accumulation of DNA damage at telomeres during cellular divisions, has been considered a main determinant of cell and organism ageing (Lopez-Otin et al., 2013; Aguado et al., 2019).

Lamin A involvement in oxidative stress response was initially suggested by the deleterious effects on oxidative metabolism elicited by lamin A/C depletion (Sieprath et al., 2015). According to the “lamin tail-ROS-buffering function” theory, the nuclear lamina acts as an intracellular ROS-sink via conserved redox-reactive cysteine residues within the lamin tail (Pekovic et al., 2011; Richards et al., 2011). Thus, in prelamin A accumulating cells, where cysteine residues are still available, free radical amount is lower than in lamin A/C null cells (Sieprath et al., 2015).

Further studies showed that, in fact, both levels of mature lamin A and amount and type of prelamin A influence the cellular antioxidant response, because lamin A and prelamin A recruit with different affinity anti-oxidant factors, as Oct-1 or the master regulator of oxidation conditions Nrf2 (Infante et al., 2014; Kubben et al., 2016). In this way, and through other mechanisms discussed in this review, stress-induced prelamin A accumulation contributes to modulate the oxidative stress response under physiological conditions. How this function is affected by progeroid lamin accumulation, with an impact on ageing processes, is discussed in the following paragraphs.

5.2. Stress response in progeroid laminopathies

Excess accumulation of prelamin A forms has been linked to delayed stress recovery and mitochondrial dysfunction (Caron et al., 2007; Mateos et al., 2013; Paradisi et al., 2005; Peinado et al., 2011; Viteri et al., 2010). Progeroid lamins cause a marked reduction in the expression of three crucial components of the mitochondrial respiratory chain including the cytochrome c, the complex IV component cytochrome C oxidase subunit I (COXI), and the complex V protein β-ATPase (Peinado et al., 2011; Rivera-Torres et al., 2013). In contrast, higher level of proteins involved in glycolysis are observed, suggesting that the accumulation of prelamin A/progerin causes a metabolic switch from oxidative to glycolytic metabolism to counteract the mitochondrial oxidative phosphorylation impairment (Peinado et al., 2011; Rivera-Torres et al., 2013). However, both the redox homeostasis alteration and the ROS increase worsen with increase of progerin amount (Richards et al., 2011; Rivera-Torres et al., 2013). A known mechanism causing defective oxidative stress response in HGPS is entrapment of anti-oxidant transcription factors. For instance, progerin accumulation affects Nrf2 nuclear translocation by entrapping the transcription factor at the nuclear lamina, thus impairing its transactivation activity towards diverse anti-oxidant molecules including proteasome subunits (Fig. 2) (Kubben et al., 2016; Ma et al., 2013; Pickering et al., 2013; Viteri et al., 2010). A similar mechanism of transcription factor retention at the nuclear envelope has been described for Oct-1, which is also involved in stress response (Columbaro et al., 2013; Malhas et al., 2009). In cells from MADA and in cellular models featuring prelamin A accumulation, Oct-1 is sequestered at the

nuclear lamina through direct prelamin A interaction and Oct-1 release is obtained by reducing prelamin A levels (Cenni et al., 2014). Rescue of oxidative stress in progeroid cells has been attempted by drug treatment either using N-acetyl cysteine or treating HGPS fibroblasts with methylene blue, with some positive results (Richards et al., 2011; Xiong et al., 2016).

5.3. DNA damage response in progeroid laminopathies

Many studies have been performed to clarify how the accumulation of lamin A precursors interferes with DDR and how, in progeroid laminopathies, damaged DNA interferes with cellular pathways (Liu et al., 2008; Gonzalo et al., 2017). Increase of DNA damage has been reported in HGPS cells by Sinensky and colleagues and it has been linked to altered functionality of some DDR factors, among which XPA, which is aberrantly recruited to DNA damage sites even in the absence of UV damage, and the double-strand DNA repair factor 53BP1, which fails to be recruited to DNA damage sites in the presence of progerin (Liu et al., 2008; Gonzalo 2017). Importantly, lamin A and prelamin A have been shown to recruit 53BP1 to the nucleus, facilitating damaged DNA repair (Gonzalo et al., 2017; Lattanzi et al., 2014). However, progerin and prelamin A accumulation to toxic levels may cause aberrant recruitment of 53BP1 and contribute to a condition of permanently activated DDR (Scaffidi and Misteli 2006; Gonzalo 2017). A condition of exacerbated DDR has been also observed at telomeres in HGPS cells and it has been linked to overexpression of specific small non-coding RNAs, which are deputed to DNA damage repair at those sequences (Aguado et al., 2019). This mechanism is further described in paragraph 7.

The DNA damage process requires transient chromatin remodeling giving access to repair factors and transient exit from the cell cycle avoiding replication of damaged sequences. These processes are mediated by several enzymes and obtained by transient upregulation of p21. In this context, we showed that prelamin A accumulation occurring during oxidative stress favors transient release of HDAC2 from the lamin-containing platform, a mechanism that elicits activation of the p21 promoter and transient upregulation of p21 (Lattanzi et al., 2014; Liu et al., 2013; Mattioli et al., 2018 and 2019). This sequence of events (Fig. 1) well represents lamin A/C function of cellular sensor, which is itself modulated by stress stimuli (eliciting prelamin A accumulation) to regulate in turn cellular response. In this scenario, the transient prelamin A increase observed during oxidative stress should be required to constrain in a limited time-frame DDR-related mechanisms. However, prelamin A modulation is abolished by progeroid lamin accumulation, causing persistent p21 upregulation and geroconversion (Leontieva and Blagosklonny, 2014; Mattioli et al., 2018). Another consequence of DNA damage is the activation of an inflammatory response. A recent study shows that DNA:RNA hybrids are formed in the cytoplasm of HGPS cells and trigger cytoplasmic DNA damage sensors cGAS and STING and downstream inflammatory response (Kreienkamp et al., 2018).

Thus, as expected in a condition of exacerbated stress response, the cell intrinsic pathogenetic events occurring in progeria elicit extracellular and systemic effects.

6. Inflammageing in progeroid laminopathies

6.1. Inflammageing in normal ageing

The term inflammageing has been introduced in year 2000 to describe a state of chronic, low-grade, sterile inflammation that characterizes old age (Franceschi et al., 2000). In subsequent years, the phenomenon has been extensively described and studied, and indicated as a possible driver of the ageing process (Kennedy et al., 2014). Moreover, it is known that many, if not all, age-associated diseases share an inflammatory pathogenesis, and therefore inflammageing is considered a risk factor for all these diseases (Franceschi and Campisi, 2014). Many events have been considered as causative of inflammageing, including nutrient excess-mediated activation of molecular pathways of inflammation (meta-flammation (Gregor and Hotamisligil, 2011)), accumulation of senescent cells endowed with a specific pro-inflammatory secretory phenotype (senescence-associated secretory phenotype, SASP (Coppe et al., 2010)), and increased production, or impaired disposal, of cellular debris that bind receptors of innate immunity (Garb-ageing, (Franceschi et al., 2017)). Of particular interest for the purpose of review is the fact that DNA damage is also able to trigger inflammation (Bonafe et al., 2012; Shen et al., 2015). Indeed, the genome instability that features laminopathies, such as HGPS, can be a cause of chronic inflammation, as DDR is emerging as a crucial trigger of pro-inflammatory and interferon response (Gunther et al., 2015; Mankan et al., 2014), and, according to the idea that inflammation is a pro-ageing mechanism, it has been recently reported that long-living people such as centenarians (that can be considered the opposite extreme of progeria patients) are endowed with a peculiar setting of elevated expression of genes devoted to the elimination of pro-inflammatory products of DNA repair (such as cytoplasmic DNA:RNA hybrids) and low level of IL-6 and IFNβ that, at local level, may facilitate their escape from the deleterious effects of age-related chronic inflammation (Storci et al., 2019). Inflammageing fits perfectly into the unifying conceptual framework that considers the ageing

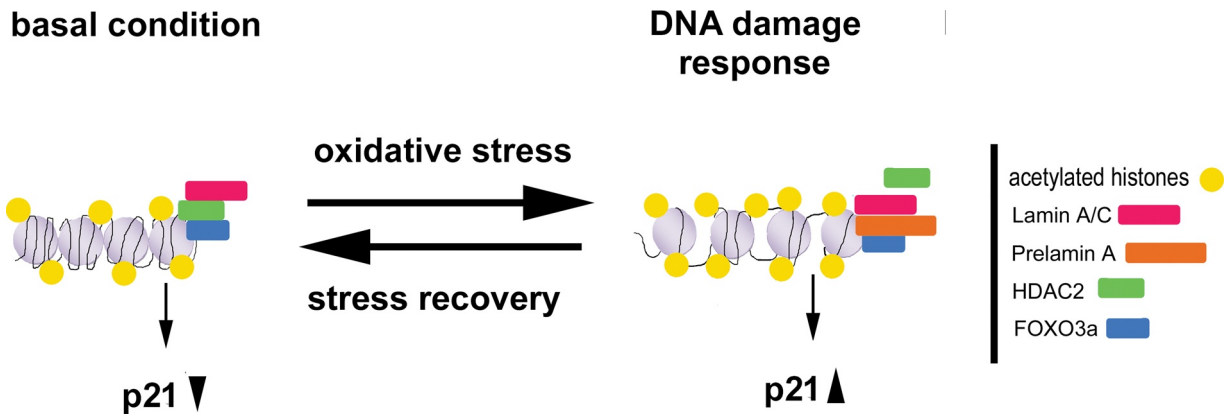

Fig. 1. Role of lamin A/C in p21 modulation through dynamic interaction with transcriptional regulators during oxidative stress response.
Under basal conditions, lamin A/C interacts with HDAC2 and recruits HDAC2 to acetylated histone substrates, causing chromatin condensation and silencing of target genes, such as p21, which is thus kept at low levels. During oxidative stress response, lamin A/C - HDAC2 interaction is reduced due to prelamin A accumulation leading to reduced recruitment of HDAC2 to acetylated histones and increased histone acetylation. As a consequence, chromatin is decondensed and p21 expression is increased. Upon recovery from oxidative stress conditions, prelamin A levels are reduced and the whole basal condition restored.

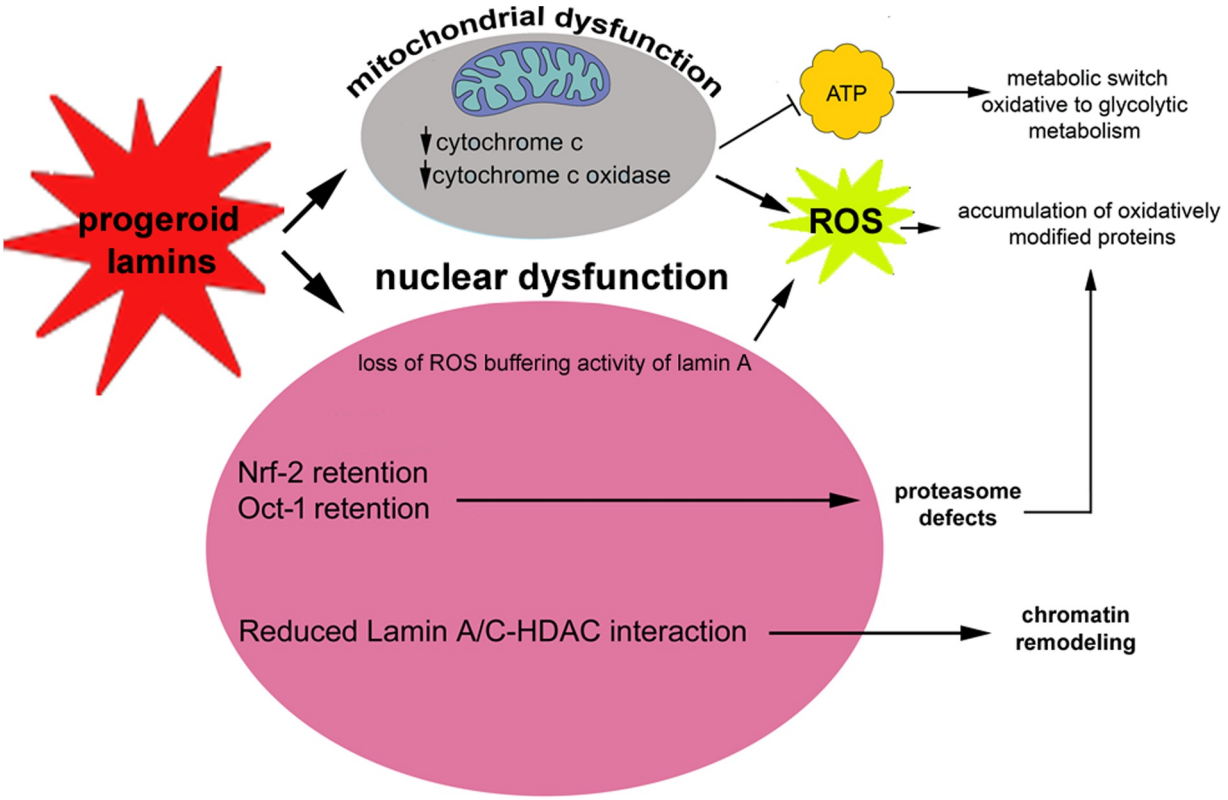

Fig. 2. Effect of progeroid lamins on antioxidant defense mechanisms.
Impairment of mitochondrial physiology, reduction of antioxidant gene expression and impaired oxidized protein degradation cause ROS increase and accumulation of oxidized molecules in progeroid laminopathy cells. Reduced lamin A/C interaction with HDAC2 (and/or SIRT1 or SIRT6) due to progeroid lamin accumulation causes aberrant chromatin decondensation and remodeling. These events favor a chronic oxidative stress condition that in turn makes prelamin A and progerin accumulating cells more susceptible to free radical injury. Nrf2: Nuclear factor erythroid 2-related factor 2; Oct1: Octamer-binding protein 1.

phenomenon as a remodeling process. In the absence of convincing evidence that ageing is a programmed phenomenon, and instead is rather the consequence of the unabated continuation of development and stress response program far beyond the timeframe envisaged by natural selection, inflammageing seems to be provided with all the features capable to explain the signs of ageing (that are present also in progeric syndromes). In fact, inflammageing is likely the consequence of an unwanted/unnecessary activation of inflammatory reactions for decades after the age of reproduction as a response to stress and in the end this low-level but continuous activation of inflammation turns to be detrimental. The presence of elevated levels of markers of inflammation (such as IL-6, IL-1 receptor antagonist, TNFα soluble receptor II) in old persons is correlated with the occurrence of typically age-associated chronic diseases, including hypertension, diabetes, ischemic heart disease, congestive heart failure, stroke, chronic obstructive pulmonary disease, cancer, Parkinson's disease, hip fracture, lower extremities joint disease, anemia, chronic kidney disease, peripheral arterial disease, and cognitive impairment (Fabbri et al., 2015; Storci et al., 2019).

The few available data suggest that also the inflammatory response may be modulated by prelamin A levels under physiological conditions, possibly as the attempt to maintain cellular homeostasis. In fact, altered cytokine levels have been linked to prelamin A accumulation in non-laminopathic cells, though under stress conditions (Liu et al., 2013). This is the case of chronic kidney disease (CKD) cells, where accumulation of prelamin A elicits secretion of excess levels of pro-inflammatory and pro-osteogenic cytokines leading to vascular calcification and artery wall senescence (Liu et al., 2013). We hypothesize that also the inflammatory response might be influenced by transient prelamin A accumulation under physiological conditions and in response to stress. This hypothesis deserves deep investigation. On the other hand, it is well-documented that progeroid lamins activate an inflammatory response typically associated with stress conditions and cellular senescence.

6.2. Inflammageing in HGPS and MADA

Here, we try to delineate how unwanted/unnecessary activation of inflammatory reactions also occurs in progeroid laminopathies due to *LMNA* mutations and accumulation of progeroid lamins. In the case of laminopathies, unscheduled prelamin A accumulation sounds as a signal of stress even in the absence of any actual stress condition. As a consequence, continuous activation of inflammatory reactions elicits organism ageing not after decades, but in a very limited time-frame. Systemic effects of mutated lamins and also of wild-type prelamin A have been suggested in diverse laminopathic conditions. For instance, a recent study performed by the Italian Network for Laminopathies in a wide cohort of patients affected by muscular laminopathies, showed up-regulation of TGFbeta 2 in the vast majority of patients, irrespective of age and disease severity, but not in unaffected mutation carriers (Bernasconi et al., 2018). TGFbeta 2 was found to be increased also in MADA osteoblasts and this condition was responsible of osteoclast activation (Avnet et al., 2011). Interestingly, inhibition of TGFbeta 2 by a neutralizing antibody reduced osteoclastogenesis and bone resorption activity, implicating TGFbeta 2 in the osteolytic process of MADA (Avnet et al., 2011). Other inflammatory cytokines have been also linked to progeroid lamins (Evangelisti et al., 2015; Osorio et al., 2012). It has been recently shown that both progerin overexpression and ZMPSTE24 depletion in human mesenchymal stem cells induce senescence through GATA-4-mediated upregulation of monocyte chemoattractant protein-1 (MCP-1) (Lee et al., 2018). In the $Lmna^{G609G/G609G}$ mouse model of progeria, the group of Lopez-Otin identified a major role of NF-kB in the induction of an inflammatory pathway mediated by

interleukin-6 (IL-6), which could be counteracted by anti-inflammatory molecules (Osorio et al., 2012). Also, in HGPS cells, progerin accumulation appears to be linked to elevated IL-6 secretion Liu et al., 2019, a condition that we recently observed both in HGPS and MADA fibroblasts (our unpublished observations). IL-6 has been shown to play a role in the hyper-activation of smooth muscle cells and it is hyper-secreted in senescent smooth muscle cells that accumulate prelamin A (Klouche et al., 1999; Liu et al., 2013). Moreover, IL-6, through its soluble receptor, induces osteogenic conversion of vascular smooth muscle cells and promotes calcification, an effect of major relevance in ageing and HGPS pathogenesis (Kurozumi et al., 2019). Finally, as mentioned above, DNA damage per se has been shown to cause an inflammatory interferon-like response in HGPS, a condition triggered by cytoplasmic DNA:RNA hybrids through cGAS and STING signaling (Kreienkamp et al., 2018). These results warrant further studies, which could improve our understanding of genetic factors that determine the onset of inflammageing. Based on reported observations, we cannot rule out that lamin polymorphisms might modulate or worsen inflammatory pathways associated with organism ageing even in the general population. On the other hand, a main reason for deepening inflammatory phenotype and the secretome in progeroid laminopathies is the availability of anti-inflammatory drugs and specific neutralizing antibodies that could be exploited for therapeutic applications (Avnet et al., 2011; Bernasconi et al., 2018).

7. microRNAs, small RNAs and progeroid laminopathies

7.1. microRNAs and small RNAs in normal ageing

MicroRNAs (miRNAs) are single-stranded 18–25nt non-coding RNAs, which are implicated in the regulation of almost all biological processes, including ageing processes and modulation of organismal lifespan (Caravia and Lopez-Otin, 2015). Among miRNAs involved in the ageing process are pro-inflammatory miRNAs and a recent work has demonstrated that low pro-inflammatory miRNAs levels are part of the molecular signature of cells from centenarians (Storci et al., 2019). Moreover, it has been demonstrated that organismal senescence is in part controlled by hypothalamic stem cells through the release of anti-ageing miRNAs in exosomes and secretion of these miRNAs declines with ageing (Zhang et al., 2017b).

Of particular interest for lamin A-linked normal and pathological ageing are miRNA-766, which down-regulates SIRT6 and miRNA-141-3p, which targets the prelamin A endoprotease ZMPSTE24 (Yu et al., 2013) (Sharma et al., 2013). Upregulation of miRNA 141-3p, which occurs during replicative senescence, has been linked to reduced HDAC1 and HDAC2 activity (Yu et al., 2013). It should be interesting to evaluate whether reduced interaction between lamin A/C and HDAC2 upon oxidative stress-induced prelamin A accumulation contributes to miRNA 141-3p upregulation, which should in turn increase prelamin A levels in a self-fueling loop (Mattioli et al., 2019). However, we suggest that miRNA 141-3p3-triggered ZPMSTE24 inhibition might contribute to finely tune prelamin A level during physiological stress response.

On the other hand, specific small RNAs have been also involved in DDR at telomeres, a condition exacerbated by progeroid lamins, as reported below (Aguado et al., 2019). Possible involvement of prelamin A in the regulation of telomeric small RNAs under stress conditions deserves further investigation.

7.2. microRNAs and small RNAs in progeroid laminopathies

Research on miRNA involvement in progeroid laminopathies revealed that several mechanisms of these pathologies are driven or prevented by miRNAs (Jung et al., 2012; Marino et al., 2010; Nissan et al., 2012; Ugalde et al., 2011b; Xiong et al., 2015; Yu et al., 2013; Zhang et al., 2017a).

In 2012, starting from the evidence that patients with HGPS, even though presenting a multisystemic disease, do not have cognitive deterioration, a phenotype commonly associated with ageing, Fong and colleagues hypothesized that the absence of brain pathology could be due to the low synthesis of progerin in the brain and demonstrated that miRNA-9, a brain-specific miRNA, downregulates lamin A and prelamin A expression in the central nervous system, in agreement with the reported absence of lamin A and progerin expression in cells of the neural lineage in vitro (Jung et al., 2012; Nissan et al., 2012). Interestingly, miRNA-9 overexpression in control or HGPS iPSCs-derived mesenchymal stem cells promoted a 38% decrease in progerin expression, while lamin C amount was increased, suggesting miRNA-9 as a potential therapeutic tool (Nissan et al., 2012).

Besides miRNA-9, the only known miRNA acting as an inhibitor of HGPS pathogenesis, several miRNAs have been identified as effectors of prelamin A-dependent ageing processes. Most data were obtained in *Zmpste24*-null progeroid mice, a model of progeroid laminopathies featuring accumulation of wild-type prelamin A.

The tumor suppressor miRNA-29a, miRNA-29b and miRNA-29c were upregulated in *Zmpste24* null progeroid mice (Ugalde et al., 2011a). Those miRNAs are upregulated during normal and pathological ageing in response to DNA damage and appear to induce the activation of p53, a condition ultimately eliciting cellular senescence (Ugalde et al., 2011a). Further, in *Zmpste24* null MEFs, miRNA-365 and miRNA-342-5p, implicated in cellular senescence and ageing-associated diseases, were upregulated (Sun et al., 2014; Xiong et al., 2015; Wei et al., 2013).

Also, miRNA-1 was upregulated in *Zmpste24*-null mice and implicated in the reduction of IGF-1 synthesis (Ugalde et al., 2010). Upregulation of miRNA-1 was confirmed in fibroblasts from HGPS patients and in cultured murine fibroblasts subjected to persistent DNA damage, which mechanistically explains the onset of the anti-ageing nutrient sensing condition of low circulating IGF-1 referred to in paragraph 3 of this review (Ugalde et al., 2010).

miRNA activity can be regulated by endogenous mRNAs, called ceRNAs (competitive endogenous RNAs), which compete for the seed region of the same miRNA thereby de-repressing all its target genes (Salmena et al., 2011). Putative *LMNA* ceRNAs have been identified by bioinformatics analysis, among which, five are involved in miRNA metabolism, others are linked to cell cycle (TP53, CDKN1A, CDC25A, and CDK6), inflammation and angiogenesis (NFKB1, IL1B, and VEGFA) (Arancio, 2012). Involvement of those ceRNAs in progeria warrants investigation.

Finally, very recent data showed upregulation of telomere-targeting small RNAs in progeroid mice and HGPS cells. These molecules, that are telomeric long non coding RNAs (tdilncRNAs) processed to telomeric DNA damage response RNAs (tDDRNAs), are produced from both DNA strands of the telomeres carrying damaged DNA sequences and are required for DDR processes at dysfunctional telomeres (Aguado et al., 2019). Interestingly, inhibition of tDDRNAs using specific anti-sense oligonucleotides improved the progeroid phenotype in mice, suggesting that an exacerbated DDR, rather than DNA damage per se, induces organismal ageing (Aguado et al., 2019). This point will be further deepened in the last paragraph of this review.

8. Mechanosignaling and progeroid lamins

8.1. Mechanosignaling in normal ageing

External stimuli relevant to ageing biology are not only those elicited by circulating factors, but also those exerted by physical stimulation, such as shear stress induced by blood flow in vessels or plasma membrane disruption occurring in osteocytes upon mechanical loading (Hagan et al., 2020; Osmanagic-Myers et al., 2019). Mechanical forces are converted into biochemical activities in the cell and influence all cellular compartments including the nucleus (Alam et al., 2014; Athirasala et al., 2017; Enyedi and Niethammer, 2016; Fedorchak et al.,

2014; Guilluy and Burridge, 2015; Osmanagic-Myers et al., 2015; Shivashankar, 2011; Swift et al., 2013). Mediators of mechanical signals are, among others, the Yes-Associated Protein (YAP) transcription factor, the Wnt/beta-Catenin signal transduction pathway and the Notch pathway (Gilbert and Swift, 2019; Hernandez et al., 2010; Mammoto et al., 2019). It has been recently demonstrated that senescent enlarged endothelial cells down-regulate YAP1 activity, reducing their own mechanosensing and proliferation ability, while stimulation and nuclear translocation of YAP1 can be obtained by reducing cell size in a constrained substrate (Mammoto et al., 2019). This very elegant experimental approach, shows an interplay between physical conditions and impaired proliferation of senescent cells, which can be unexpectedly reverted by modifying the extracellular environment. However, most evidences linking mechanosignaling to the ageing process come from studies performed in progeria models. It has been proposed that nuclear lamins may globally function as a "mechanostat" i.e. a structure able to react to environmental changes and to answer by adapting the tissue stiffness to running environmental requirements in terms of mechanical resistance (Kirby and Lammerding, 2018; Osmanagic-Myers et al., 2015). In particular, recent studies attributed to chromatin the role of resisting small deformations and to nuclear lamins the role of withstanding/responding to large deformations (Stephens et al., 2017). A key element in mechanosensing is the LINC complex, a dynamic and finely tuned protein platform at the nuclear envelope, which establishes bridges between the nucleoskeleton and diverse cytoplasmic structures, including the actin cytoskeleton, intermediate filaments and specialized structures such as the centrosome (Meinke et al., 2014). Among LINC components, a regulatory role is mainly exerted by SUN1, which is a nuclear envelope transmembrane protein directly binding lamin A/C (Mattioli, 2011; Meinke, 2014). SUN1 is a key regulator of nuclear movement that influences centrosome positioning and cell migration (Meinke et al., 2014). Both centrosome positioning and nuclear movement are altered in fibroblasts from old individuals in a SUN1-dependent manner and, since both factors impact on cell migration, they may contribute to the ageing phenotype (Chang et al., 2019). These cellular defects occur in aged cells because SUN1 levels are elevated (Haque et al., 2010; Lattanzi et al., 2014; Chang et al., 2019). Prelamin A plays a major role in SUN1 increase, as it both stabilizes and upregulates the LINC component (Mattioli et al., 2011). Moreover, prelamin A targets ERK1/2 and nesprin 2, another LINC complex constituent, at promyelocytic leukemia bodies (PML), in response to DNA damage (Warren et al., 2015). Thus, the LINC complex and prelamin A act as mechanosignaling transducers upon stress stimuli by compartmentalization of ERK1/2. It is conceivable that persistent accumulation of prelamin A associated with high SUN1 levels and nesprins 2 relocalization at PML convert a DDR condition into a senescence pathway. In strong support of this hypothesis, and mostly of a major role of SUN1 in prelamin A-triggered mechanisms affecting lifespan, downregulation of SUN1 expression significantly increased longevity in a murine model of HGPS, the *LmnaΔ9* mouse (Chen et al., 2012). These and most likely other LINC components are involved in ageing-associated mechanosignaling, and we cannot rule out the existence of a spectrum of molecular sensors at the nuclear envelope, possibly interacting with prelamin A in a tissue-specific way, implicated in the ageing process (Worman and Schirmer, 2015).

8.2. Progerin effects on mechanosignaling

Progerin impacts on diverse nuclear and cellular pathways affecting mechanosignaling. In HGPS cells, nuclear stiffness is increased and chromatin compaction is reduced (Columbaro et al., 2005; Mattioli et al., 2018; Stephens et al., 2017; Stephens et al., 2018). It is possible that any variation in stiffness/viscosity of the nucleus has important consequences because the mechanical deformation of nuclear components influences per se protein unfolding, accessibility for enzymes and nuclear response to stimuli (Buxboim et al., 2014; Swift et al., 2013). Moreover, it has been reported that in the presence of progerin there is a complex combination made of a stiffened nucleoskeleton and softened nuclear interior due to chromatin decondensation, which impairs a regular response to mechanical signals, associated with loss of proper interaction between nucleoskeleton and LINC complex (Booth et al., 2015; Hale et al., 2008).

The ability to form complexes containing lamin A/C and its partners involved in mechanosignaling is heavily threatened in progeroid nuclei, a condition that in turn affects mechanosignaling (Capanni et al., 2009; Wu et al., 2014). Emerin is a main lamin A/C-binding partner at the nuclear membrane and interacts with actin and actin-associated proteins, i.e. it participates in the constitution of the nuclear peripheral functional network (Holaska et al., 2004; Lattanzi et al., 2003). The LINC complex is also severely affected in HGPS cells. In fact, progerin accumulation induces an increase of SUN1, as also occurs when prelamin A is accumulated in MADA cells (Camozzi et al., 2012; Haque et al., 2010). Importantly, LINC complex disassembly relieves progerin-induced nuclear structure alterations in smooth muscle cells and vessel walls (Chen et al., 2012; Kim et al., 2018). It appears that releasing the LINC-mediated connection between nuclear envelope and cytoplasm can prevent altered force transduction into the nucleus caused by progerin-dependent increase in nuclear stiffness (Booth et al., 2015; Haque et al., 2010). As described above for normal aged fibroblasts, impaired nuclear movement has been described in HGPS cells and directly linked to progerin expression and SUN1 increase: of note, reducing progerin farnesylation rescued the whole mechanism, highlighting a major role of progeroid lamins (farnesylated prelamin A forms) in ageing-related mechanosignaling pathways (Chang et al., 2019).

Further, direct link between progeroid lamins and altered extracellular matrix (ECM) affecting fibroblast proliferation has been reported. Wnt signaling is disrupted in post-natal mouse fibroblasts carrying *Lmna Δ9* or *Lmna Δ50* mutations, which are causative of progeroid phenotype (Hernandez et al., 2010). Altered Wnt signaling affects in turn ECM composition, and culturing cells on a "wild-type ECM" rescues cellular defects (Hernandez et al., 2010). Of note, culturing cells on single ECM components was not sufficient to rescue the cellular phenotype, suggesting that a well-balanced (possibly lamin-directed) composition of the ECM is necessary to avoid cellular senescence.

Very recently, experimental evidence has been provided that progerin accumulation reduces eNOS expression in endothelial cells, leading to interstitial fibrosis in myocardium and vascular endothelium (Osmanagic-Myers et al., 2019). The mechanism is sustained by an impairment in nucleo-cytoskeleton coupling, in particular an altered F-/G-actin ratio caused by progerin accumulation and downstream effects on the LINC components, which coexists with a deregulation of mechanoresponsive myocardin-related transcription factor-A (MRTFA) (Osmanagic-Myers et al., 2019).

Progerin has been also involved in altered nucleo-cytoplasmic transport. It has been reported that a main player in this process, transportin 1, is sequestered on microtubules of progerin expressing cells, through a mechanism involving the N-acetyltransferase NAT10, which targets alpha tubulin, with deleterious consequences on the import of nuclear pore complex proteins (Larrieu et al., 2018). Interestingly, not only inhibition of NAT10, but also reducing microtubule stability, rescued transportin 1 shuttling from the cytoplasm into the nucleus and nuclear recruitment of its cargoes (Larrieu et al., 2018). Although the mechanism linking progerin expression to NAT10 impairment is still elusive, these results highlight another progeroid lamin-driven mechanism of protein sequestration leading to impaired nuclear import, in addition to those involving Nrf2 and Oct-1 sequestration.

Finally, an interesting lamin A/C-mediated mechanism of epigenetic response to mechanical stimulation has been identified. In MSC, lamin A/C has been found to mediate mechanical strain-induced changes in HDAC activity and histone acetylation (Li et al., 2011). It will be

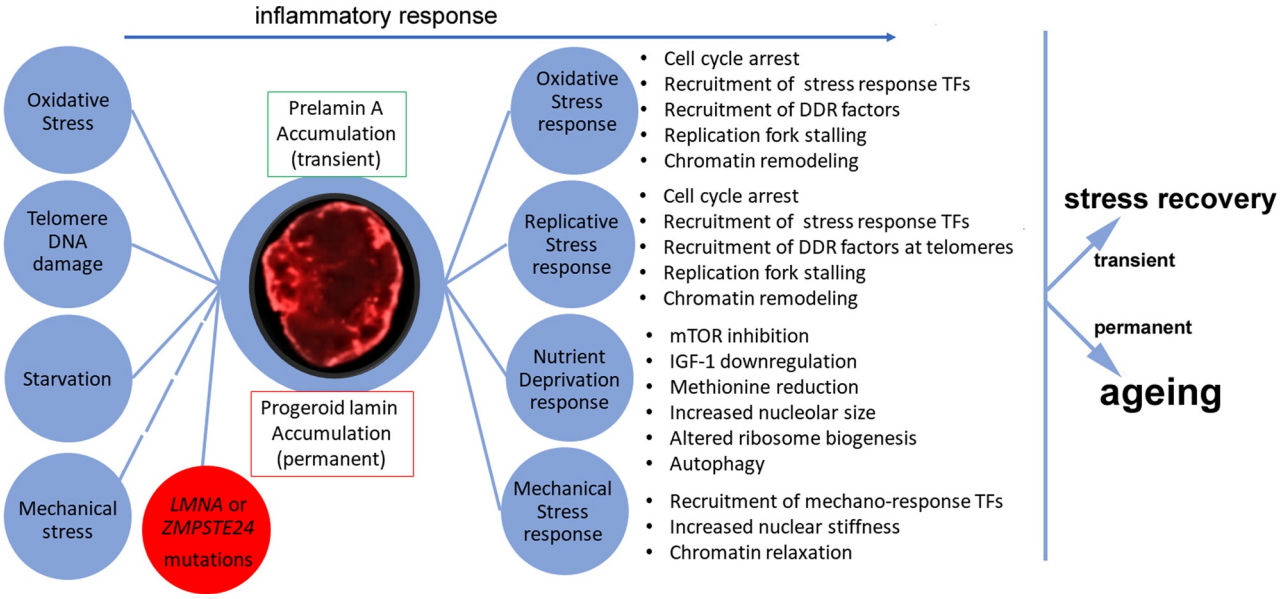

Fig. 3. Ageing-related stress response mechanisms triggered by prelamin A accumulation. Different types of stress conditions, including, but not limited to, those represented in the left blue circles, trigger accumulation of prelamin A. As indicated in the upper green box, under physiological conditions, prelamin A accumulation is transient and it is abolished upon stress recovery. *LMNA* or *ZMPSTE24* mutations (red circle) elicit permanent progeroid lamin accumulation (lower red box), which is the pathogenetic condition of progeroid laminopathies. An HGPS nucleus accumulating progerin is shown in the immunofluorescence microscopy image. Prelamin A accumulation influences the stress response pathways depicted in the right circles. In detail, chromatin remodeling would occur through lamin A/prelamin A-mediated modulation of epigenetic enzymes; transcriptional activity of key cell cycle and stress response genes, above all p21, would be increased; replication fork stalling and cell cycle arrest would occur; recruitment of DDR factors (including tDDRNAs) would accelerate DNA damage repair; mTOR inhibition increasing autophagic clearance of damaged molecules and rewiring of nutrient sensing pathway would set the metabolic status to a condition avoiding interference of stress factors with the normal metabolic pathways; prelamin A would increase nuclear stiffness and elicit cytoskeleton and ECM remodeling to protect nuclear structure from mechanical insults (Aguado et al., 2019; Hernandez et al., 2010; Kreienkamp et al., 2018; Mattioli et al., 2018; Osmanagic-Myers et al., 2019). Depending on the transient or permanent condition of prelamin A accumulation cells are recovered from stress and keep their proliferation or differentiation condition (stress recovery) or hold the stress response mode thus entering senescence (ageing).

interesting to test whether altered acetylation-dependent response to mechanical loading might occur in progeroid laminopathies due to progeroid lamin-dependent reduction of lamin A/C-HDAC2 interaction (Mattioli et al., 2018).

In conclusion, altered LINC complex organization, ECM or actin cytoskeleton composition and defective import of mechanosignaling regulators into the nucleus appear to contribute to the senescent phenotype in the presence of progeroid lamins. We hypothesize that these mechanisms could be part of a cellular strategy aimed at adaptation of the timing of some transcriptional activities under stress conditions. It will be interesting to test nuclear envelope-prelamin A interplay in cells from old individuals to assess the relevance of these pathways to the normal ageing process.

9. Conclusions

Our hypothesis on lamin A role in ageing processes, based on the whole evaluation of data summarized in this review, is represented in Fig. 3.

We propose that, under physiological conditions, lamin A acts as sensor of environmental and cell intrinsic changes. In response to oxidative or replicative stress, starvation conditions and probably mechanical stimulation, reduced rate of prelamin A maturation induces an increase of prelamin A levels. Accumulated prelamin A triggers various pathways involved in stress response, which are promptly inhibited upon stress recovery. Prelamin A-driven mechanisms delay some cellular activities in order to allow rescue of potentially dangerous conditions as DNA damage or accumulation of dysfunctional molecules. The efficiency of this system is ensured by the prompt resetting of cells to a non-stress mode, which is obtained by restoring the basal rate of prelamin A maturation after stress recovery (Lattanzi et al., 2014; Liu et al., 2013; Mattioli et al., 2019). Under pathological conditions determined by progeroid lamins, a stress response mode is permanently set in cells, which causes cellular senescence. An increasing number of senescent cells will then elicit organism ageing, as occurs in progeroid laminopathies.

In agreement with this hypothesis, several studies performed in progeroid animal models or HGPS cells show that stress response pathways considered anti-ageing mechanisms and observed in long-lived individuals are unexpectedly triggered by progerin expression. In fact, low mTOR activity and autophagy, reduced IGF-1 levels, active DDR (including DDR at telomeres) are observed in HGPS cells and animal models. Most importantly, inhibition of such mechanisms rescues some progeroid phenotypes and prolongs survival (Kreienkamp et al., 2018; Ibrahim et al., 2013; Aguado et al., 2019).

The above described lamin A-driven mechanisms rely on the particular feature of prelamin A of being available at low levels in cells and promptly increasing its own availability through inhibition of its post-translation cleavage upon diverse stimuli. This condition can ensure basal level of prelamin A interplay with stress response factors and/or rapid increase of such interplay, without any involvement of transcriptional processes, to promptly activate stress response (Lattanzi et al., 2014; Liu et al., 2013). The increase of prelamin A levels during cellular differentiation, as demonstrated in muscle cells, could take advantage of this particular feature and could be also aimed at reducing potentially dangerous conditions during myotube formation (Capanni et al., 2008; Mattioli et al., 2011). Moreover, it is tempting to speculate that prelamin A-driven mechanisms here described could be part of a more complex lamin-dependent regulatory mechanism aimed at cyclic activation/inactivation of diverse cellular responses (Maraldi, 2018). In this context, accelerated ageing is associated with permanent setting of a stress response mode in cells, which is determined by loss of prelamin A dynamics due to persistence of progeroid lamins. Thus, prelamin A appears to be one of the few molecules, such as p53 and p21, that are

set to stably elevated levels to convert a protective pathway into a senescence pathway. Such fundamental functions might explain the existence of an enzyme as ZMPSTE24, whose activity is possibly only aimed at prelamin A processing Barrowman et al., 2012.

Even in non-laminopathic pathological conditions, repeated stress stimuli may cause excess accumulation of prelamin A, as described in smooth muscle cells from patients affected by CKD, a disorder characterized by progressive vascular disease, systemic inflammation, muscle wasting and frailty (Shanahan, 2013). It will be interesting to unravel the mechanism(s) underlying tissue-specific or whole organism accumulation of prelamin A upon repeated environmental changes, as well as to understand to which extent prelamin A-triggered ageing pathways are activated at local (tissue-specific) rather than systemic level (Liu et al., 2013; Lattanzi et al., 2014). Our current knowledge suggests that there must be signaling mechanisms targeting *ZMPSTE24* gene to down-regulate its expression under stress conditions, possibly through upregulation of miRNA 141-3p (Lattanzi et al., 2014; Yu et al., 2013). However, the whole regulatory pathway is still unknown. New knowledge in this field could provide therapeutic targets for progeroid laminopathies and other ageing-associated diseases. In the whole scenario here proposed, inflammation may be activated as a tool to rapidly propagate stress signals. In the scheme depicted in Fig. 3, inflammatory signals could be activated by stress conditions, as damaged DNA, by molecules involved in stress response and even by accumulated prelamin A. Thus, inhibition of inflammatory pathways, as demonstrated in a few studies, might alleviate, if not solve, the hyperactivation of stress response pathways elicited by progeroid lamins. Based on these considerations, a strategy to counteract premature ageing could be to combine anti-inflammatory drugs with inhibitors of hyperactivated stress response pathways, although avoiding progeroid lamin accumulation remains a major goal.

Author Contributions

All of the authors contributed to the writing and editing of the article.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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