Biochemical and Biophysical Research Communications 421 (2012) 635–639

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Mini Review

Lamins as mediators of oxidative stress

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ARTICLE INFO

Article history:
Received 9 April 2012
Available online 17 April 2012

Keywords:
LAMIN A/C
Oxidative stress
ROS

ABSTRACT

The nuclear lamina defines both structural and functional properties of the eukaryotic cell nucleus. Mutations in the LMNA gene, encoding A-type lamins, lead to a broad spectrum of diseases termed laminopathies. While different hypotheses have been postulated to explain disease development, there is still no unified view on the mechanistic basis of laminopathies. Recent observations indicate that laminopathies are often accompanied by altered levels of reactive oxygen species and a higher susceptibility to oxidative stress at the cellular level. In this review, we highlight the role of reactive oxygen species for cell function and disease development in the context of laminopathies and present a framework of non-exclusive mechanisms to explain the reciprocal interactions between a dysfunctional lamina and altered redox homeostasis.

1. Introduction: form and function of the nuclear lamina

The nuclear envelope (NE) is a double lipid bilayer that physically separates the nuclear contents from the cytoplasm; only allowing regulated bidirectional transport at the nuclear pore complexes. The inner nuclear membrane is directly connected to the nuclear lamina, a dense fibrous network of intermediate filament proteins called lamins [1]. Two classes of lamins exist: A-type lamins (lamin A & C) and B-type lamins (lamin B1 & B2). Lamins A and C are alternative splice products of the LMNA gene, whereas lamins B1 and B2 are products from two separate genes. The nuclear lamina has a multitude of functions, the most prominent one being its role in providing mechanical support for the nucleus [2]. Next to this structural role, an accumulating body of evidence indicates that the nuclear lamina modulates gene expression either by directly interacting with chromatin, or by (conditionally) sequestering transcriptional regulators at the nuclear periphery [3–5]. Other functions involve signal transduction, cell cycle control and DNA repair mechanisms [6–8]. Mutations in genes encoding components of the nuclear lamina, mostly LMNA, lead to a class of diseases called laminopathies. Disease manifestations are very diverse, ranging from tissue-specific pathologies such as muscular dystrophies and lipodystrophies, to systemic disorders such as Hutchinson-Gilford Progeria Syndrome (HGPS) [1]. Despite this diversity, laminopathies share several features on the cellular level, including misshapen nuclei, disorganization of heterochromatin and defects in the DNA damage response pathway [9]. After transcription and translation of LMNA, a prelamin A is formed which is further processed to lamin A in four distinct steps: (1) farnesylation, (2) removal of the last three amino acids, (3) carboxymethylation and finally (4) removal of the last 15 amino acids, including the farnesyl group [10]. Most laminopathies arise from defects in this posttranslational maturation process which often leads to an accumulation of intermediate prelamin A isoforms. One well-documented example is HGPS, which is associated with a mutation in the lamin A/C gene (LMNA) that results in an activation of a cryptic splice site in the LMNA transcript, causing a deletion of 50 amino acids in exon 11. This inhibits the final cleavage step and leads to the accumulation of a permanently farnesylated mutant lamin A protein, called progerin [11].

2. Reactive oxygen species and oxidative stress

Reactive oxygen species (ROS) are small, short lived molecules that mediate various cellular responses including cell proliferation, differentiation, gene expression and migration [12]. Excessive accumulation of ROS however, can lead to DNA damage and the buildup of irreversibly oxidized proteins [13,14]. The term oxidative stress refers to a state of the cell where the production of ROS is higher than the removal of ROS, which is either due to increased production of ROS or reduced antioxidant defenses. The major intracellular sources of ROS are the mitochondria and the NADPH oxidases (NOX). Whereas mitochondria mostly produce ROS as a byproduct of the oxidative phosphorylation [15], NADPH oxidases directly catalyze the production of superoxide (O_2^-) [16].

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0006-291X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbrc.2012.04.058

To counter the potential damaging effects of ROS, cells have evolved several antioxidant systems, including ROS defusing enzymes like catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPX), as well as non-enzymatic systems comprising glutathione (GSH) and Vitamins (A, C and E) [17].

Cells respond to oxidative stress by altering gene expression. Apart from their direct damaging effects to coding sequences [13], ROS can alter gene expression through epigenetic and genetic mechanisms. Whereas the epigenetic mechanisms mainly concern alterations in DNA-methylation patterns [18], the genetic mechanisms rely on the activation of various redox-sensitive transcription factors, such as Rb, p53, FoxO and NF-κB [19]. These regulatory proteins become activated by an oxidative signal in the cytoplasm after which they translocate into the nucleus. There, specific cysteine residues within the DNA-binding domain of each transcription factor are reduced by thioredoxin 1 and redox factor-1. This reduction is necessary for transcription-factor binding to DNA and subsequent gene activation. Thus, oxidants in the cytoplasm activate redox signaling, whereas oxidative stress in the nuclear compartment blocks this process [20].

3. Laminopathies are correlated with oxidative stress at the cellular level

Recent data point to a relationship between lamin mutations and altered ROS metabolism. Both A-type and B-type lamins seem to have a dual function in this respect, both as sensors and as elicitors of oxidative stress. Elevated levels of ROS and an increased sensitivity to oxidative stress have been reported in cells from patients suffering from many different laminopathies associated with LMNA mutations and prelamin A accumulation. A few examples are: Dunnigan-type familial partial lipodystrophy (FPLD) [21] and other lipodystrophies [22], Amyotrophic quadricipital syndrome with cardiac involvement [23], Autosomal dominant Emery Dreifuss muscular dystrophy (AD-EDMD) [14], HGPS [24] and Restrictive dermopathy (RD) [24]. In particular, the farnesylated form of prelamin A seems to induce excessive ROS and protein oxidation [22,24]. Reduction of the levels of mature lamin A and the presence of aberrant prelamin isoforms also alter the levels of antioxidant enzymes. Reduced levels of CAT and GPX were observed in HGPS fibroblasts [25], while elevated levels of SOD, CAT and GST were found in lamin deficient patient fibroblasts ($LMNA^{Y259X/Y259X}$) [14,26].

Oxidative stress also affects lamin structure. Oxidation of conserved cysteine residues in the tail domain of mature lamin A appears to perturb its function and promote cellular senescence and susceptibility to ROS [14].

Next to the involvement of A-type lamins, increasing evidence also suggests a role for B-type lamins in oxidative stress. Exposure to oxidative stress induces lamin B1 accumulation in a p38-MAPK dependent manner [27]. Plausibly, lamin B1 attempts to decrease the ROS levels by regulating stress-responsive gene expression. But under conditions of chronic oxidative stress lamin B1 eventually decreases and fails to prevent senescence. Indeed, downregulation of lamin B1 has been shown to alter the expression of several anti-oxidants either through regulation of Oct1 or p53 [4,28].

Downstream effects of ROS, specifically in the context of laminopathies, include protein oxidation, telomere shortening and persistent DNA damage [6], ultimately converging in a state of cellular senescence. It is well established that there is an exponential correlation between cellular oxidative stress levels and telomere shortening rates [29]. Increased telomere shortening has also been observed in several human fibroblast cell lines overexpressing different mutant LMNA variants. Interestingly, overexpression of wild-type LMNA also causes accelerated telomere shortening [30]. Telomere shortening in turn is known to induce premature cell cycle arrest by activation of p53 (tumor suppressor), thereby promoting senescence. p53 then represses PGC-1α and PGC-1β, both master regulators of mitochondrial physiology and metabolism [31]. This way, a direct reinforcing loop is initiated of increased ROS, telomere shortening and impaired mitochondrial function.

It has also been shown that, under oxidative stress conditions, telomerase, the major enzyme for telomere length homeostasis, can translocate from the nucleus to the cytosol and the mitochondria to exert a regulatory role in apoptosis [32,33]. Furthermore, telomerase appears to repress ROS-dependent cellular responses to tumor necrosis factor-α without affecting NF-κB activation [34].

In the context of laminopathies, ROS have also been linked with persistent DNA damage. DNA double-strand breaks, induced by ROS are repaired efficiently in normal human fibroblasts, but appear to be unrepairable in HGPS fibroblasts. These breaks are a major cause of the poor growth of the HGPS fibroblasts since adding N-acetyl cysteine, a ROS scavenger, to the culture medium reduces DSBs and markedly improves population doubling times [13].

4. Lamin-dependent mechanism of oxidative stress response

Although, as described above, there are many indications for a link between a dysfunctional lamina and disturbed redox biology, the underlying pathways remain poorly understood. In this section a framework comprising of several non-exclusive mechanisms is postulated, based on the various functions of lamins in cellular physiology. A simplified overview is given in Fig. 1.

A dysfunctional lamina can arise from mutations in the lamin-coding genes and in the genes responsible for the processing of prelamin A. We refer to this hereditary form of dysfunction as *innate lamina dysfunction*. Lamina perturbation can also originate from drug treatments such as anti-retroviral protease inhibitors (HIV-PIs) that, as a side effect, also block ZMPSTE24, the metallopeptidase that removes the terminal 15 amino acids in the fourth processing step of prelamin A [10] or it can originate from irreversible (oxidative) damage to normal mature lamins [14]. We refer to this type of dysfunction with the term *acquired lamina dysfunction*. It has been suggested that lamin A acts as a ROS-sink inside the nucleus, protecting other, less abundant and more critical proteins from transient, mild oxidative damage [14]. This has also been reported for other abundant structural proteins inside the cytosol like actin [35]. Lamins, however can only buffer up to a certain critical level, such that chronic or highly acute oxidative stress induces irreversible oxidative damage to some conserved cysteine residues leading to a dysfunctional lamina as demonstrated in Fig. 2. [14].

A dysfunctional lamina, innate or acquired, may influence ROS in several ways. It is known that the lamina serves as a docking station inside the nucleus, but presumably also in the cytoplasm, e.g. through components of the LINC complex, a mechanical connection between the nucleo- and cytoskeleton involved in signaling pathways and gene regulation [36]. Inside the nucleus this docking function results in gene regulation, either by *direct* interactions with chromatin or transcriptional complexes or *indirect* via interaction with transcription factors. As for *direct* interactions, lamins play a key role in intranuclear positioning and compaction of chromosomal domains [37]. Aberrant chromatin organization has been observed in various conditions of abnormal lamin expression: lamin deficiency as well as overexpression of progerin leads to the depletion of heterochromatin and abnormal nuclear morphology [38,39]. This may induce activation of repressed genes and alter DNA binding of transcription factors and regulatory proteins. Indeed, in HeLa cells expressing different disease inducing LMNA mutations, DNA damage repair is perturbed due to incorrect localization of ATR

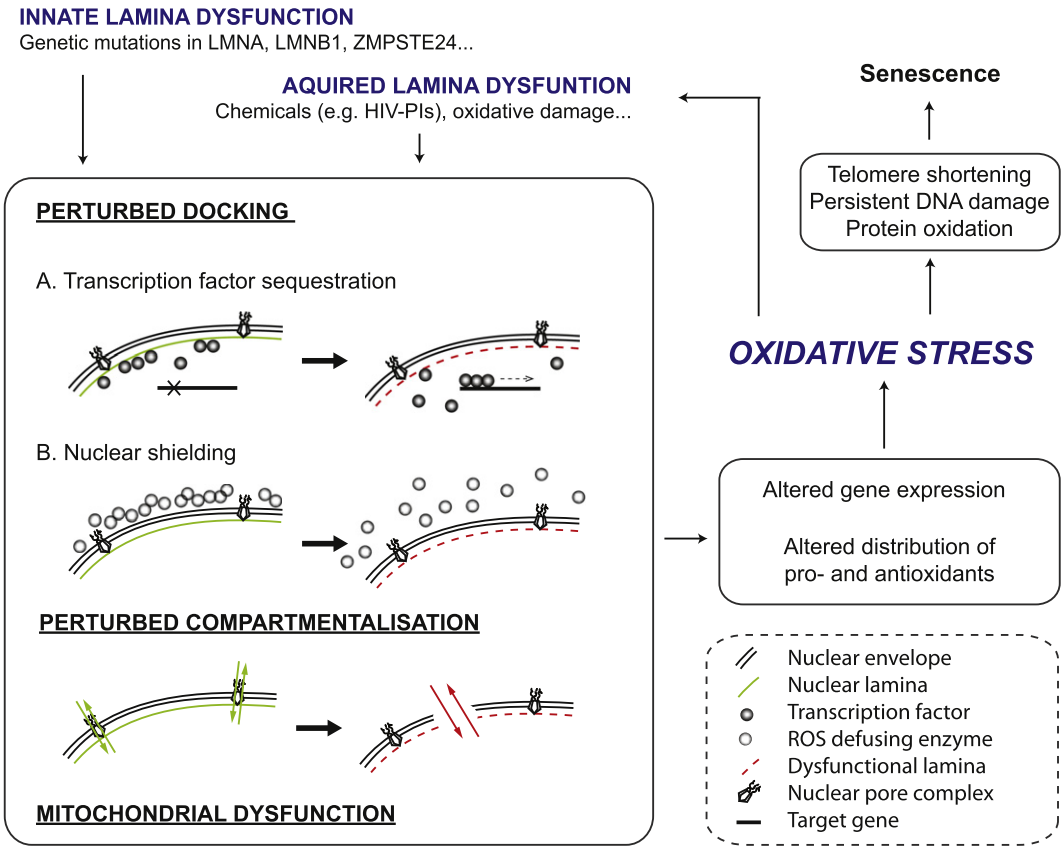

Fig. 1. Framework for reciprocal interactions between lamins and oxidative stress. Genetic (innate) or non-genetic (acquired) mechanisms cause lamina dysfunction, which leads to an altered affinity (docking) for redox-responsive transcription factors and/or ROS defusing enzymes, reduced compartmentalization potential (ruptures) or mitochondrial dysfunction. This causes changes in stress-responsive gene expression and/or spatial redistribution of pro- (mitochondria, NOX) and anti-oxidants (CAT, SOD...), inducing a state of oxidative stress. Chronic oxidative stress induces telomere shortening, protein oxidation and persistent DNA damage, eventually heralding cellular senescence. See text for more details.

[40]. It was proposed that this mislocalization is caused by disturbed lamin-chromatin interactions. *Indirect* influence of the lamina on gene expression can mostly be brought back to the reversible associations of lamins with a multitude of redox-responsive transcription factors including Rb, SREBP1 and Oct1 [5,41]. In lamin B deficient mouse embryonic stem cells (MEFs), the transcription factor Oct-1, is no longer properly sequestered at the nuclear lamina. This leads to an increase of free Oct-1 inside the nucleus and higher expression of genes that are involved in oxidative stress response such as GPX3, IL-6 and SOD1 [4]. Conversely, in LMNA knockout MEFs as well as in lamin A/C deficient patient cells (Y259X/Y259X), repetitive ruptures of the nuclear membrane lead to a temporary and local translocation of nuclear Oct-1 from nucleus to cytoplasm [26]. This lowers the concentration of free Oct-1 inside the nucleus and, has opposite downstream effects on Oct1-dependent gene expression compared to the lamin B deficient cells [26]. Nevertheless, both $Lmna^{-/-}$ and $Lmnb1^{\Delta/\Delta}$ MEFs eventually show elevated ROS levels and higher susceptibility to oxidative stress compared to wild type cells, pointing to a delicate balance between pro- and antioxidants in regulation of the oxidative stress response.

From the cytoplasmic side, changes can occur in spatial concentration of ROS defusing or generating enzymes [42]. Recently Fabrini et al. [43] postulated the presence of a nuclear shield, a 300 nm thick perinuclear hyper-crowding of protective enzymes, among which ROS defusing enzymes like CAT, GPX and GST are highly represented, up to seven times higher than in the cytosol. It concerns mainly cationic enzymes that assemble through electrostatic interactions. The role of this shield could be the protection of the nuclear DNA against oxidative stress. To induce assembly, the anionic nesprin 1 and nesprin 2 were postulated as charge-counterparts and scaffolding proteins. These giant proteins directly link the actin cytoskeleton to the nuclear lamina via the LINC complex [36]. Lamin A/C is essential for proper nesprin 2 localization at the nuclear membrane [44] so absence of normal and/or presence of mutant lamin A can disturb proper formation of this nuclear shield, leading to a local decline of antioxidants around the nucleus which could in turn elicit a higher susceptibility to oxidative stress.

Next to a perturbed docking function, a dysfunctional lamina can also cause repetitive and transient disruptions of the nuclear envelope [26]. This leads to an intermixing of cytoplasmic and nuclear components, ranging from small diffusible molecules such as transcription factors to large macromolecular complexes such as PML bodies and mitochondria. Indeed, in patient cells of several different laminopathies, functional mitochondria were observed inside the nucleoplasm [26,45]. Obviously the close proximity of these ROS-sources to genomic DNA greatly increases the risk of oxidative damage and senescence. This is indirectly demonstrated by the fact that mitochondrial DNA (mtDNA) shows increasing amounts of damage with increasing age, likely attributed to the proximity of the mtDNA to the source of ROS [46]. Mitochondria are not the only ROS sources that could become displaced, another potential source is NADPH oxidase 4 (NOX4), which contributes to superoxide (O_2^-) and H_2O_2 generation, and has been shown to colocalize with lamin A/C, especially after hepatitis C virus infection [47,48].

Recent data also point to a relationship between lamins and mitochondrial dysfunction. Cells, which accumulate farnesylated prelamin A, (either due to LMNA mutations or HIV-PI therapy),

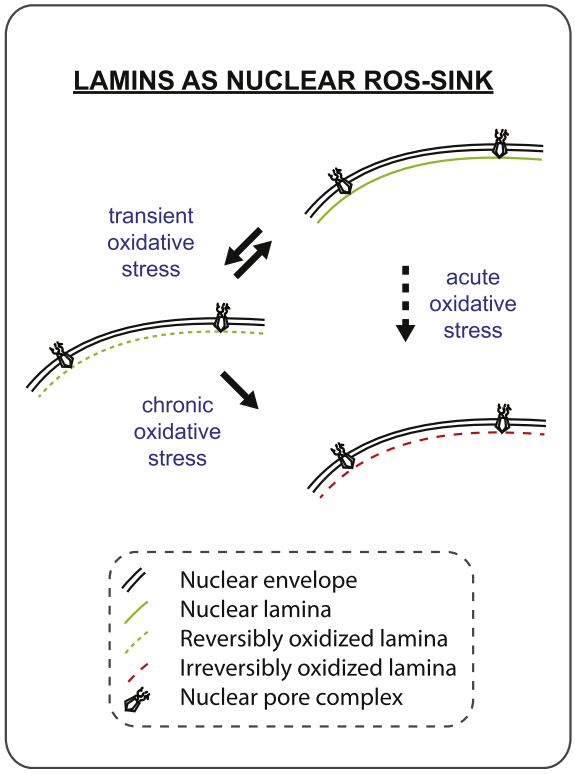

Fig. 2. The lamina as a ROS sink [14]. Conserved cysteine residues of A-type lamin proteins can become reversibly oxidized under conditions of mild oxidative stress. Chronic or highly acute oxidative stress induces irreversible oxidative damage leading to an acquired dysfunctional lamina.

show a lowered expression of the mtDNA encoded subunit II of the cytochrome oxidase complex IV (COX 2). This disrupts the electron transport chain, lowering the mitochondrial potential, perturbing ATP production and generating ROS [22]. It is not yet known, whether the downregulation is caused by direct interactions with prelamin isoforms or due to reduction in functional lamin A. Similarly, after silencing of lamin B1, the expression of the mitochondrial SOD2 gene decreases [28] and the expression of p53, which plays a central role in mitochondrial oxidative phosphorylation, increases [49]. A whole organism study on Zmpste24$^{-/-}$ mice, which accumulate farnesylated prelamin A, also shows an increased mitochondrial response to oxidative stress, further supporting the relationship between defective prelamin A processing and mitochondrial dysfunction [50].

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