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REVIEW

Role of the nuclear envelope in the pathogenesis of age-related bone loss and osteoporosis

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The nuclear envelope is the most important border in the eukaryotic cell. The role of the nuclear envelope in cell differentiation and function is determined by a constant interaction between the elements of the nuclear envelope and the transcriptional regulators involved in signal transcription pathways. Among those components of the nuclear envelope, there is a growing evidence that changes in the expression of A-type lamins, which are essential components of the nuclear lamina, are associated with age-related changes in bone affecting the capacity of differentiation of mesenchymal stem cells into osteoblasts, favoring adipogenesis and affecting the function and survival of the osteocytes. Overall, as A-type lamins are considered as the 'guardians of the soma', these proteins are also essential for the integrity and quality of the bone and pivotal for the longevity of the musculoskeletal system.

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Introduction

Eukaryotic cells are characterized by a compartmentation structure that divides the intracellular space in two different regions, the nucleus and the cytoplasm.[1] This compartmentation is maintained by the nuclear envelope, which is a perinuclear cisterna of the endomembrane system and is constituted by the inner nuclear membrane (INM) and the outer nuclear membrane (ONM) enclosing a lumen ('perinuclear space') (**Figure 1**). The integrity of this structure is interrupted by the nuclear pore complexes (NPC), which span both the inner and the outer membranes and are the portal between the nucleus and the cytoplasm.[1–3]

Owing to the continuity between the nuclear envelope and the endoplasmic reticulum, the main functions of the ONM are very similar to those of the endoplasmic reticulum.[4] In contrast, the INM is in close interaction with the nuclear lamina, multiple nuclear proteins and chromosomes,[2] having an essential role in cell differentiation, organization of chromatin and communication with the extranuclear cytoskeleton.[2,5]

Recent evidence has emerged demonstrating that the nuclear lamina, a network of intermediate filament proteins,[6] is not only closely associated with the INM (**Figure 1**) but is also an important determinant of its function and interactions. The intermediate filament proteins that compose the nuclear lamina are known as lamins,[5,6] the lamin gene family in mammals includes three different genes that encode seven different proteins (lamin A, AΔ10, C, C2, B1, B2 and B3). Most adult mammalian somatic cells contain the three major lamins A, B1 and C. These various forms are grouped into two classes, A-type (A, AΔ10 and C) and B-type (B1 and B2). Although B-type lamins are found in all nucleated somatic cells, the expression of A-type lamins is developmentally regulated.

A-type lamins have been recently linked to a number of human progeroid syndromes and adult-onset degenerative diseases;[6–8] therefore, in this review we will focus on the role of A-type lamins in bone cells particularly in the age-related changes that predispose to osteoporosis and fractures. By reviewing this evidence, we will propose that modulating the expression of A-type lamins in the musculoskeletal system could become a new therapeutic intervention to prevent age-related bone loss and osteoporosis.

Age-related Bone Loss and Osteoporosis

With increasing age, there is a significant reduction in bone formation. This is mostly due to a shift from osteoblastogenesis to

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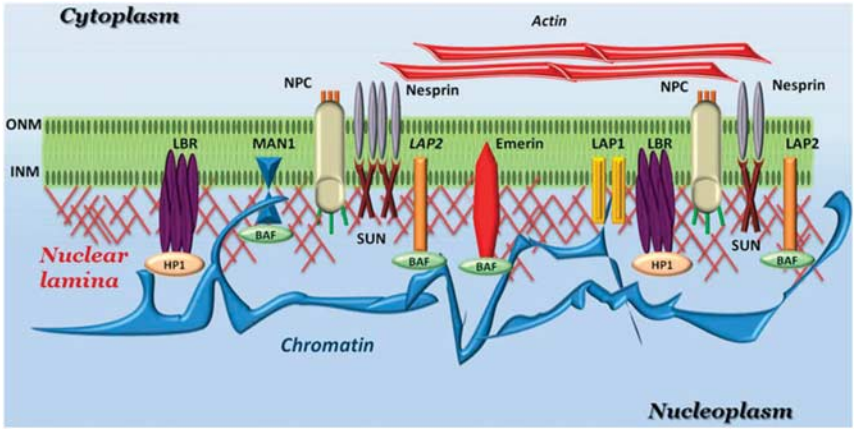

Figure 1 The nuclear envelope is composed of the nuclear membranes, nuclear lamina and NPC. The ONM is continuous with the rough endoplasmic reticulum and generally similar in composition. The INM is associated with the nuclear lamina and the chromatin. Integral proteins of the INM such as lamin B receptor (LBR), MAN1, SUNs, emerin, lamina-associated polypeptide 1 (LAP1) and transmembrane isoforms of lamina-associated polypeptide 2 (LAP2) bind to components of the lamina and chromatin (adapted with permission from Méndez-López and Worman[3]).

predominant adipogenesis in the bone marrow.[8–10] In addition to these changes in mesenchymal stem cells (MSC) differentiation, old bones show other features such as high number of apoptotic osteocytes and osteoblasts, decreasing levels of growth factors and increasing levels of adipokines.[10] In addition, the mechanosensing function of the osteocytes is also affected by aging, thus decreasing their capacity to regulate bone formation.[11]

Overall, these age-related changes in bone are the consequence of defective somatic maintenance and repair and decreasing response to stress, which are the main components of the 'disposable soma' theory. This theory proposes that the strongest candidates for longevity genes are those that protect the somatic cells during their lifetime.[12] It is then assumed that, in the case of bone, those genes that protect MSC, osteoblasts and osteocytes from age-related changes would protect bone quality and decrease the likelihood of suffering osteoporosis and fractures.

A-type Lamins as the Guardians of the Soma

Maturation of the lamin A/C precursor (known as prelamin A) into lamin A/C is a sophisticated process that involves farnesylation by farnesyl transferase (FT), endoproteolysis by ZMPSTE24 and methylation (**Figure 2**),[7] resulting in mature lamin A, which is approximately 2 kDa less than prelamin A.[13]

The proposed parallel functions of the nuclear envelope are summarized in **Figure 3**. Owing to the constant interplay between A-type lamins and signal transduction pathways, transcription factors and chromatin-associated proteins in somatic cells, it has been proposed that A-type lamins are the 'guardians of the soma' and that alterations in the interactions between A-type lamins and the proteins of the nuclear envelope could be determinant in the normal aging process and in the pathogenesis of multiple age-related diseases.[5,7]

In fact, the best example of the importance of A-type lamins in health and disease has been obtained from patients with mutations in the *LMNA* gene, which encodes lamin A and lamin C. *LMNA* mutations have been associated with a group of diseases known as laminopathies, which include those progeroid syndromes in which the primary compromise involves striated

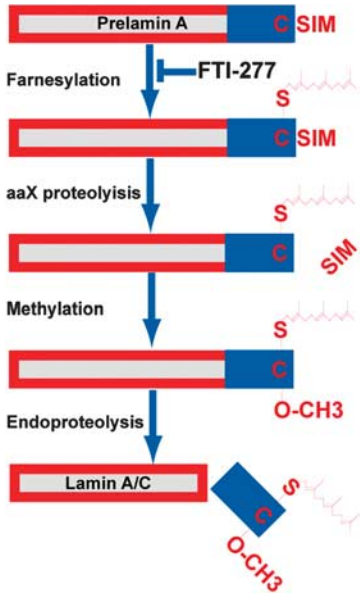

Figure 2 Processing of prelamin A into lamin A/C.

muscle, adipose, bone and neuronal tissues.[5,7] Interestingly, homozygous *Lmna* knockout mice (*Lmna*$^{-/-}$)[14] and *Zmpste24* knockout mice (*Zmpste24*$^{-/-}$)[15] not only share a shorter lifespan but also show defects in a similar group of organs and systems. Taken together, this evidence underscores the importance of A-type lamins in the development and maintenance of the soma and supports the hypothesis that *LMNA* is a candidate to be classified as a longevity gene.

A-type Lamins and Aging

Among the multiple mutations in the *LMNA* gene,[5] the mutation identified by Levy *et al.*[16] in 2003 in patients suffering from Hutchinson Gilford progeria syndrome (HGPS) was critical to establish the link between A-type lamins and aging. Although there is still some controversy whether HGPS is a pure example of accelerated aging, patients with HGPS (estimated prevalence one in 8 million) show a characteristic phenotype that

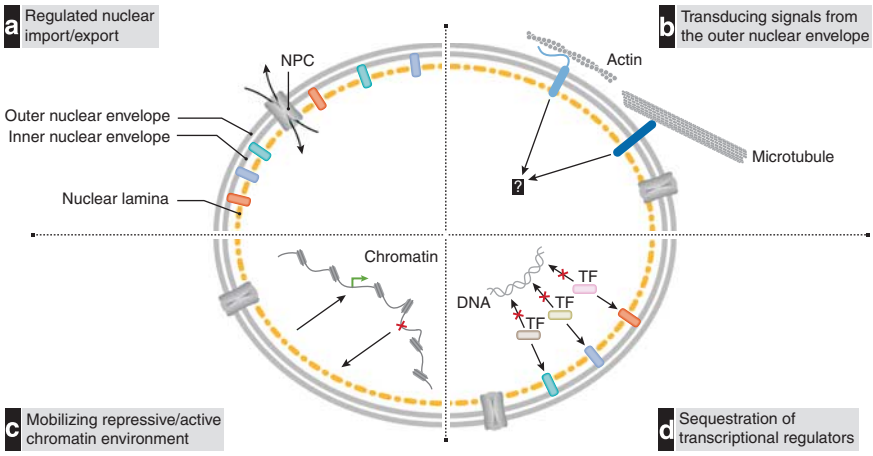

Figure 3 Functions of the nuclear envelope in regulating gene expression. Proposed parallel functions of the nuclear envelope in regulating gene expression (adapted with permission from Heessen and Fornerod[2]).

includes early growth retardation, short stature, lipodystrophy, alopecia, stiff joints and atherosclerosis.[17] Interestingly, a common feature in these patients is their significant and accelerated bone loss, which predisposes them to repeated non-healing fractures.[17,18]

The HGPS phenotype is the consequence of accumulation of progerin, a mutant form of lamin A.[13] The mutation responsible for this accumulation is a recurrent, *de novo*, dominant point mutation (C1824T) in the *LMNA* gene that leads to a 50-residue truncation of the lamin A protein. This truncated lamin A retains the CAAX motif but lacks the second proteolityc cleavage site of ZMPSTE24.

Both *Lmna*$^{-/-}$ and *Zmpste24*$^{-/-}$ mice show a progeroid phenotype with similar features to laminopathies in humans.[15,16] In the case of *Lmna*$^{-/-}$ mice, their life span is extremely short (about 6 weeks) due to severe cardiac and muscle defects.[16] In contrast, *Zmpste24*$^{-/-}$ mice survive longer (~6 mo) although their lifespan is reduced when compared with wild-type (WT) counterparts.[16] Nevertheless, as in humans, both murine models of defective lamin A/C show accelerated aging associated with significant compromise in several tissues, particularly those of mesenchymal origin.

As it is unclear how HGPS relates to normal aging, studies looking at the role of lamin A in the physiological aging process have been recently performed. A study by Scaffidi and Misteli[19] looking at multiple skin fibroblasts cell lines from old (81–96 years) individuals, consistently showed nuclear aberrations similar to those seen in HGPS cells in clear contrast with cells obtained from young individuals. Cells obtained from both young and old donors exhibited increased defects with prolonged passage, but these changes occurred more rapidly in cells obtained from old donors, consistent with observations in HGPS patient cells in which the nuclear defects accumulate during passage in culture. Interestingly, in the same study, a striking change in lamin A/C localization was detected in cells of old donors. In contrast to the cells of young individuals that showed a substantial fraction of lamin A/C present throughout the nucleoplasm, this fraction was almost completely absent in the cells of old donors, with most of their lamin A/C accumulating in the nuclear rim.

Our group found a very similar pattern in the hearts of normal-aged C57BL6 mice.[20] In these mice, and additionally to lower levels of lamin A/C expression in old cardiomyocytes, we found changes in the distribution of lamin A/C in the nucleus in the older group. Although the significance of age-related changes in lamin A/C distribution remains unknown, lower and abnormally distributed lamin A/C in aging cells would affect the interaction between lamin A/C, the nuclear proteins and transcription factors essential for the normal function of the longevity machinery.

A-type Lamins, Age-related Bone Loss and Osteoporosis

After the discoveries that the *LMNA* gene was affected in HGPS and that osteoporosis was a prominent feature in both humans and animal models, it was tempting to hypothesize that lamin A/C has a role in the pathogenesis of age-related bone loss and osteoporosis. To summarize the new evidence on the role of lamin A/C in bone biology, we will review the current knowledge on the function of lamin A/C in every particular type of bone cells.

A-type lamins in MSC. In bone, aging affects the number and confluence of MSC niches.[21,22] Owing to both intrinsic changes and an inappropriate bone marrow milieu, MSC decrease their capacity to differentiate into osteoblasts and therefore predominantly differentiate into adipocytes.[9,10] The mechanism of this differentiation shift of MSC in aging bone remains poorly understood with some groups proposing that the age-related changes in MSC differentiation could be associated with oxidative stress,[11] progressive DNA damage[23] or defective telomerase activity.[24]

Owing to the essential role of lamin A/C as a 'guardian of the soma' and the evidence that most of the organs affected by lamin A/C deficiency are from mesenchymal origin, it has been proposed that the lamin A/C abnormalities could predispose to some of the age-related changes observed in MSC.[19] In fact, the phenotypic features observed in patients with laminopathies support this hypothesis.

Furthermore, the role of lamin A/C in the aging process of MSC has been associated with alterations in the telomeres.[24] Changes in lamin A/C distribution also affect the distribution of telomeres, which cluster in intranuclear foci containing lamin A/C, a feature that has been associated with senescence and apoptosis. In addition, an abnormal nuclear lamina influences MSC number and replicative potential.[19]

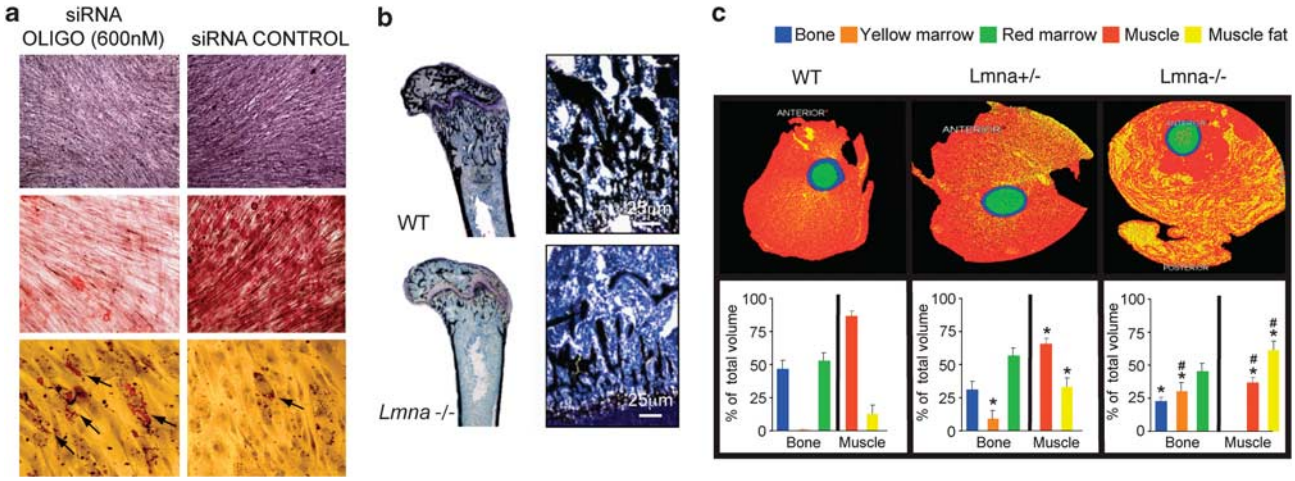

Figure 4 Effect of lamin A/C deficiency in bone and muscle. (**a**) Lamin A/C knockdown of MSC *in vitro* inhibits osteoblastogenesis, as demonstrated by lower levels of osteoblast differentiation (upper panels, alkaline phosphatase staining) and decreased mineralization (middle panels, alizarin red staining). In addition, low levels of lamin A/C are also associated with high levels of adipogenesis (lower panels, oil red O staining) (adapted with permission from Akter *et al.*[24]). (**b**) Von Kossa staining of distal femur obtained from Lmna$^{-/-}$ mice show significantly lower bone mass than their WT controls (adapted with permission from Li *et al.*[28]). (**c**) Noninvasive quantification of fat infiltration in bone and muscle of Lmna$^{+/-}$ mice. The figure shows higher levels of fat infiltration in both muscle and bone of the mutants as compared with their WT controls. There is also a significant reduction in bone and muscle mass in the mutant groups (adapted with permission from Tong *et al.*[33]).

In a recent article on the role of lamin A/C in adult stem cell maintenance and tissue regeneration, Pekovic and Hutchinson[22] performed a very comprehensive review of all the interactions between lamin A/C and transcription factors required in MSC differentiation. The authors proposed that lamin A/C regulates stem cell maintenance via a range of regenerative signaling pathways and that the regulation of adult stem cells aging may occur at several levels that intersect with lamin A/C such as progerin and prelamin A.

Role of A-type lamins in osteoblast differentiation and function. The important role of lamin A in osteoblast differentiation has been recently characterized both *in vitro* and *in vivo*. *In vitro*, our team has recently reported that lamin A/C knockdown affects osteoblast differentiation and function (**Figure 4**).[25] Using a model of lamin A/C siRNA in osteogenic differentiating human MSC, we reported that siRNA-treated MSC showed a higher incidence of nuclear changes and lower osteoblast differentiation. In addition, lamin A/C knockdown reduced Runx2 nuclear-binding activity, which is a critical step in osteoblastogenesis.

The same year, Rauner *et al.*[26] reported similar results. In their study, the authors also studied bone marrow stromal cells exposed to lamin A/C siRNA. They reported a 26% impaired osteoblast differentiation associated with decreased levels of expression of Runx2 and osteocalcin and lower expression of alkaline phosphatase activity.

In terms of *in vivo* evidence, the original report on the phenotype of *Zmpste24*$^{-/-}$ mice by Bergo *et al.*[15] described spontaneous fractures, low bone mass and muscle weakness in these mice that lack mature lamin A. We further analyzed this bone phenotype[27] and reported that *Zmpste24*$^{-/-}$ mice have accelerated features of age-related bone loss including lower osteoblast and osteocyte numbers and higher levels of marrow adipogenesis.

However, the bone phenotype observed in *Zmpste24*$^{-/-}$ mice is associated with accumulation of unprocessed prelamin A and cannot be directly compared with the lamin A siRNA model previously tested *in vitro*. Therefore, a model with low levels of lamin A/C expression would be more appropriate to be compared with the *in vitro* data. Using a murine model of autosomal dominant Enery–Dreifuss muscular dystrophy 2 caused by a missense L530P *LMNA* variant that affects lamin A/C expression, Mounkes *et al.*[28] reported that homozygous L530P/L530P mice developed features of progeria that included significantly lower bone mineral density as compared with their heterozygous and WT counterparts. However, the mechanisms of bone loss and the potential association between lamin A/C deficiency and osteoporosis were not fully explored.

Subsequently, our group reported the bone phenotype of the *Lmna*$^{-/-}$ mice that was developed by deleting exons 8–11 of the *Lmna* gene, which disrupts both lamin A and C isoforms. These mice show a dystrophic condition related to Enery–Dreifuss muscular dystrophy 2, including the appearance of skeletal and cardiac muscle alterations and perturbations of the nuclear envelope.[14] At birth, *Lmna*$^{-/-}$ mice are identical to their heterozygous and WT controls. After birth, *Lmna*$^{-/-}$ mice show accelerated features of aging. The most common cause of short life span and premature death in *Lmna*$^{-/-}$ mice is cardiovascular complications due to dilated cardiomyopathy. Our results demonstrated that *Lmna*$^{-/-}$ mice are severely osteopenic and show low levels of bone turnover associated with a decrease in bone formation that exceeds the decrease in bone resorption, clearly mimicking the cellular changes of senile osteoporosis.[29]

In addition to our demonstration that lamin A/C is required for osteoblastogenesis and bone formation both *in vitro* and *in vivo*, we further explored whether lamin A/C expression is decreased in normal aging osteoblasts. Comparing lamin A/C expression in osteoblasts of young (4mo) and old (24mo) C57BL6 mice, we found that levels of lamin A/C expression were significantly reduced in the older group.[30] In fact, this finding was also extended to the chondrocytes, which also showed a decline in lamin A/C expression with aging.

Role of A-type in bone marrow adipogenesis As lipodystrophy is a frequent feature observed in laminopathies, several

studies have investigated the role of lamin A/C deficiency in adipocyte differentiation.[31,32] The most widely studied mechanism is the interaction between prelamin A and sterol-regulatory binding protein 1 (SREBP1). Prelamin A and SREBP1 co-localize in the nuclear rim, which coincides with the downregulation of PPARγ expression. Therefore, it is thought that prelamin A limits the access of the transcription factor SREBP1 to the nuclear interior. Furthermore, overexpression of prelamin A could also repress the expression of PPARγ, which questions the necessity of SREBP1 sequestration in the nuclear lamina.[32] In fact, this co-localization is not exclusive of prelamin A but could also involve processed lamin A. A recent study by Douband-Goulet *et al.*[33] reported that variation of A-type lamin protein level and spatial organization, in particular due to disease-linked mutations, influences the sequestration of SREBP1 at the nuclear envelope and thus contributes to the regulation of SREBP1 function.

As most of the evidence on the role of the nuclear lamina in adipogenesis has been obtained from non-bone cell lines, we tested whether accumulation of prelamin A in MSC using a FT inhibitor (FTI-277) would also affect adipogenesis. Our results indicate that FTI-277 inhibits adipogenesis in MSC by affecting PPARγ expression and activation.[34]

Furthermore, we also tested whether decreasing levels of mature lamin A/C have an effect on adipogenesis both *in vitro* and *in vivo*. Our siRNA model of lamin A/C knockdown of MSC showed increasing adipogenesis concomitant with decreasing osteoblastogenesis[25] (**Figure 4**). Additionally, both *Zmpste24*$^{-/-}$ and *Lmna*$^{-/-}$ mice showed higher levels of bone marrow adipogenesis.[27,29]

A particularly interesting finding in *Lmna*$^{-/-}$ mice was that increasing levels of marrow fat infiltration and low bone mass closely correspond with high levels of fat infiltration in muscle.[35] With the growing interest on the interactions and shared biological pathways in muscle and bone, decreasing levels of lamin A/C in aging emerges as a possible common mechanism to explain age-related osteopenia and sarcopenia, which are also associated with high levels of fat infiltration.

Role of A-type lamins in the osteocytes. Osteocytes are the most numerous cells found in mature bone composing >90% of the bone cell population. Osteocytes function as mechanosensors and thus regulate other cell functions to maintain a good bone quality and strength.[36] Lamin A/C is required in mechanotransduction in several tissues.[37] In the heart, the presence of lamin A/C is critically required for the structural integrity of the cardiomyocyte nucleus and cytoskeleton.[38] In other models, lamin A/C deficiency is associated with impaired nuclear mechanics thus increasing nuclear deformations and fragility, attenuating expression of mechanosensitive genes, and impairing viability of mechanically strained cells.[39]

There is recent evidence suggesting that lamin A/C is also required in the mechanotransduction function of the osteocytes. A recent proteomic analysis has provided new evidence in terms of identifying some of the molecular mechanisms used by osteocytes for embedding in matrix, forming dendritic processes, and protecting themselves within a hypoxic environment.[40] Interestingly, among those proteins identified in this proteomic analysis, lamin A/C was identified as one of the osteocyte-selective proteins.[40]

To test whether lamin A/C is required in the anabolic effect of exercise on bone, a typical condition of mechanical stimulation and bone formation, we exposed *Lmna*$^{+/-}$ male mice to strenuous maximal exercise for 6 weeks.[41] Histomorphometry analysis showed a significant increase in bone volume fraction (BV/TV) in exercised vs sedentary WT mice. In contrast, exercised *Lmna*$^{+/-}$ mice showed a significant reduction in microarchitecture as compared with sedentary *Lmna*$^{+/-}$ controls, including trabecular and cortical thinning. In addition, we found a significant increase in bone cell number in exercised vs sedentary WT mice, whereas exercised *Lmna*$^{+/-}$ mice showed a significant reduction in osteoblasts and osteocytes number as compared with sedentary *Lmna*$^{+/-}$ controls. Finally, levels of activated β-catenin in osteoblasts and osteocytes were significantly decreased, whereas sclerostin expression was increased in exercised *Lmna*$^{+/-}$ mice as compared with exercised WT controls. Our data indicated that the presence of lamin A/C is required for the anabolic effect of exercise on bone having an important role on the regulation of mechanosensing protein expression.

Role of A-type lamins in osteoclasts. In their *in vitro* analysis, Rauner *et al.*[26] reported that lamin A/C inhibition in bone marrow stromal cells increased receptor activator of nuclear factor kappa-B ligand mRNA and protein levels, whereas osteoprotegerin (OPG) expression was decreased, resulting in an increased receptor activator of nuclear factor kappa-B ligand/OPG ratio; thus, enhancing their ability to support osteoclastogenesis, as reflected by a 34% increase of tartrate-resistant acid phosphatase (+) multinucleated cells. In addition, treatment of monocytes with FTI-277 facilitated their differentiation towards the osteoclastic lineage. On the other hand, the bone resorption activity of osteoclasts obtained in the presence of high prelamin A levels is lower with respect to control osteoclasts.[42]

In contrast to the *in vitro* evidence, our *in vivo* data obtained from *Zmpste24*$^{-/-}$ and *Lmna*$^{-/-}$ mice[27,29] showed contradictory results. *Zmpste24*$^{-/-}$ mice have high osteoclast number whereas *Lmna*$^{-/-}$ mice show low number and 'aberrant' forms of osteoclasts, suggesting that although high levels of prelamin A could stimulate osteoclastogenesis, absence of lamin A/C affects osteoclast differentiation and function.

The Nuclear Envelope as a Therapeutic Target for Osteoporosis

When considering manipulation of lamin A/C as a therapeutic approach for osteoporosis, both prelamin A processing and lamin A/C expression could become potential therapeutic targets.

Previous studies in cells from individuals with HGPS have shown that FTI improve nuclear abnormalities associated with prelamin A accumulation, suggesting that although this effect could be related to the effect of FTI on a broad range of targets, these compounds could represent a therapeutic approach for this progeroid syndrome in the future.[43] Furthermore, a recent study treated *Zmpste24*$^{-/-}$ with a combination of pravastatin and zoledronic acid.[44] Both compounds efficiently inhibit both farnesylation and geranylgeranylation of progerin and prelamin A. The investigators reported that this combination markedly improves the aging-like phenotypes of *Zmpste24*$^{-/-}$, including growth retardation, loss of weight, lipodystrophy, hair loss and bone defects. Similarly, the longevity of these mice was substantially extended.

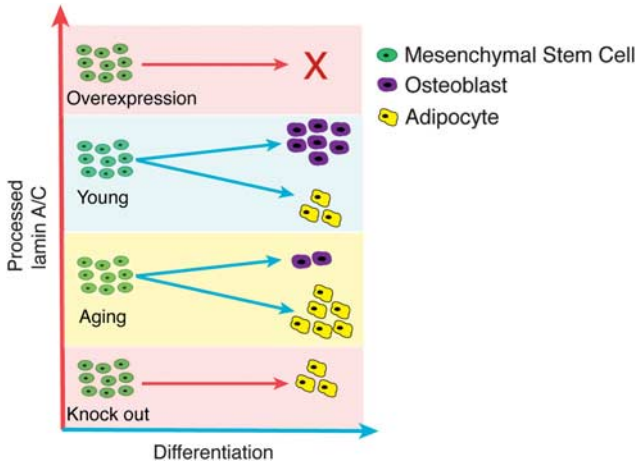

Figure 5 A proposed hypothesis of the role of lamin A/C in MSC differentiation. Lamin A/C deficiency (as in knockdown conditions) inhibits osteoblastogenesis and facilitates adipogenesis. In young bone, normal levels of processed lamin A/C are associated with predominant MSC differentiation into osteoblast in the bone microenvironment. In old bone, low levels of lamin A/C are associated with a predominant adipocyte differentiation of MSC. Finally, overexpression of lamin A/C inhibits MSC differentiation into either osteoblast or adipocytes.

Our team explored the therapeutic potential of increasing lamin A/C processing in MSC.[45] Human MSC were induced to differentiate into osteoblasts while treated with either FTI-277 or alendronate, an anti-resorptive reported to stimulate osteoblastogenesis *in vitro*.[46] Strikingly, and in contrast to its effect as inhibitor of geranylgeranylation in osteoclasts, MSC treated with alendronate showed high levels of prelamin A farnesylation and thus higher lamin A/C expression. This effect was associated with higher levels of osteoblastogenesis in the alendronate-treated cells after induction of lamin A processing by alendronate, an effect that seems to be dependent on a direct effect of alendronate on FTase. In contrast, treatment of MSC with FTI-277 induced higher levels of unprocessed prelamin A and affected their capacity to differentiate into osteoblasts. This experiment suggests that stimulation of lamin A/C farnesylation in differentiating MSC is a promissory therapeutic target to stimulate osteoblastogenesis and inhibit adipogenesis in bone.

Conclusion

In this review, we have summarized most of the current evidence on the role of the nuclear lamina, an important component of the nuclear envelope, in the pathophysiology of age-related bone loss and osteoporosis. Lamin A/C seems to have a role in every critical pathway in bone metabolism including cell differentiation, function and survival. **Figure 5** summarizes the current knowledge on the role of lamin A/C in MSC differentiation.

There are still multiple unresolved questions in this field. Overall, the nuclear envelope has been recently described as a 'transcription factor-resting place' by interacting with most of the transcription factors that pass through the NPC and in some cases sequestering them to prevent their further action.[2] In addition, other proteins of the nuclear envelope, which also interact with osteogenic transcription factors, deserve further exploration.

In conclusion, the understanding of the intrinsic mechanisms of normal aging in bone is essential to develop novel therapeutic targets for osteoporosis. In this case, lamin A/C fulfills the criteria as a strong longevity gene that regulates bone mass and bone turnover. Increasing lamin A/C processing in MSC of aging bone is an attractive approach to increase bone formation and prevent osteoporosis. In addition, the benefits of increasing lamin A/C levels are not limited to bone, as decreasing levels of lamin A/C in other systems such as muscle and cartilage could have a role in other age-related degenerative diseases.

Conflict of Interest

The authors declare no conflict of interest.

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