

## New look at the role of progerin in skin aging

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### Abstract

Current literature data indicate that progerin, which is a mutant of lamin A, may be one of several previously known physiological biomarkers of the aging process which begins at the age of 30. Lamins belong to the family of intermediate filaments type V and are an important component of the nuclear envelope (NE). The physiological processes of an alternative splicing of *LMNA* (lamin A/C) gene and posttranslational processing result in the formation of different variants of this gene. Prelamin A is generated in cytosol and modified by respective enzymes. In the final step, 15-aa peptide is released at the C-terminus, resulting in mature lamin A. Point mutation of cytosine to thymine at position 1824 in exon 11 of *LMNA* gene causes a truncated form of lamin A, which is defined as progerin. In the course of time, progerin is mainly found in skin fibroblasts and reticular layers of terminally differentiated keratinocytes. Changes take place in the nucleus and they are similar to those observed in patients with Hutchinson-Gilford progeria syndrome and refer mainly to an increase in the amount of reactive oxygen species which reduce the level of antioxidant enzymes, DNA damage and histone modification. There are still pending studies on working out new anti-aging strategies and the skin is the main area of research. Biomimetic peptides (analogues of elafin) are used in cosmetics to reduce the formation of progerin.

**Key words:** biomarker, progerin, lamins, progeria, skin aging.

### Introduction

Genes encoding antioxidant proteins, DNA repair genes, genes encoding helicases, genes encoding anti-tumor protein, genes connected with regulators of energetic substances (insulin metabolism, regulation of growth) and genes encoding telomerases are responsible for skin aging. Lifestyle greatly affects the skin and might substantially contribute to skin aging. Ultraviolet radiation is a common factor responsible for the process of skin aging [1]. Up to now, there have been many studies on that process. In some of them the authors compared the natural process of aging with Hutchinson-Gilford progeria syndrome (HGPS), which is a genetically conditioned disease. That disease is caused by a mutation in lamin A, which is a fibrillar protein and a component of the nucleus. A mutant form of this protein is called progerin. Fibroblasts of dermis and keratinocytes were taken from healthy people and from patients with HGPS, and were used during studies. Progerin interacts with cell environment and causes changes in the location and level of chromatin remodeling factors, transcription factors, DNA repairing factors, factors connected with the nuclear lamina. By decreasing a level of antioxidant proteins and activation of proteasome it leads to changes in the morphology of the nucleus, structure of chromatin and gene expression.

All of these factors influence cell hyperproliferation and cause an arrest of the cell, apoptosis and result in dysfunction of tissue and organs [2]. There are also other biomarkers of skin aging such as lipofuscin and lactic acid, which are results of dysfunctional cell processes. Many beauty therapies, gel preparations or creams are applied in cosmetology. They are enriched with appropriate components, which makes the skin firm, inhibits the process of aging, reduces discolourations and prevents the skin from becoming flabby and wrinkled.

### Occurrence, structure and activity of lamins

Lamins are fibrillar proteins which belong to a family of intermediate filaments of type V. They contain the  $\alpha$ -helical central rod domain, short N-terminal head domain and C-terminal tail domain. The rod domain contains four  $\alpha$ -helical coils, which are separated with short non-helical sequences. In the tail part of the protein conservative nuclear localization signal, highly conservative immunoglobulin – fold domain and CaaX motif (C-cysteine,  $\alpha$ -aliphatic amino acid, X-amino acid residue) can be found. Non-polymerized lamins are dimers and they can polymerize to structures such as head to tail or by unparallel dimers which aggregate in tetramers and polymerize to thick fibers. Lamin filaments

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are organized in three-dimensional nuclear lamin, which is a mechanical support for nuclear envelope (NE) and a protection for genetic material. There are three genes, which encode lamin: *LMNA*, *LMNB1* and *LMNB2*. An alternative splicing of mRNA and post-translational processing lead to different variants of these genes. Lamins A, C, C2, AΔ10 are isoforms of expression of the *LMNA* gene, which consists of 12 exons. Lamins are an important component of a nucleus, because they create a nuclear lamina, protect genetic material before mechanical forces and that decides about the shape, size and location of the nucleus. They also contribute to the right location of pore complexes and link of cytoskeleton with nuclear skeleton, as well as transcription and replication. They probably take part in physiological aging, mitosis, cell differentiation, cancerogenesis, apoptosis and influence the course of virus infections. Lamin A, which is formed in cytosol as prelamina A plays an important role in progeria. Posttranslational modification of prelamina A lasts about three hours (Fig. 1) [3, 4]. At the beginning it is modified by farnesyltransferase and a farnesyl isoprenoid is added to cysteine at C-terminus. Afterwards, a farnesylated prelamina A is modified by an endoprotease called RAS converting enzyme 1 (RCE1) (specific for prenyl-caax), which cuts the last three amino acids at C-terminus. The next phase included an esterification of farnesylcysteine with the methyl group at the C-terminus by isoprenylcysteine carboxyl methyltransferase (ICMT). Farnesylated prelamina A is hydrolyzed by metalloprotease dependent on zinc ions (ZMPSTE24) and a 15-amino acid section at C-terminus is released. It results in obtaining unfarnesylated lamin A. Diseases, which are connected with mutations in genes encoding lamins and other proteins which are components of the nuclear envelope and interact with lamins such as emerin, spectrin repeat containing nu-

clear envelope 1 (SYNE1), inner nuclear membrane protein man 1 (MAN1), lamin B receptor (LBR) are called laminopathies. Lamins A/C play a role in cancerogenesis because in complex with LAP2α they control the activity of growth suppressor pRb and in complex with emerin they play a role in activity of β-catenin. A complex of lamin A with MAN1 interacts with SMAD as an antagonist of TGF-β [3, 5].

Many studies were conducted to check whether an accumulation of prelamina A variants causes changes in lamin A location and influences its expression. It was then observed that a differentiated accumulation of lamin variants depends on its post-translational modifications and influences the growth and morphology of the membrane. This, in turn, influences the functioning of the nucleus. In case of lack of mutation in lamin A, a decreased activity of enzymes involved in modification pathway of prelamina A will cause cell dysfunction and allows for age pathologies [6]. An application of farnesyltransferase inhibitors (FTI) or overexpression of gene which encodes ZMPSTE24 will have an influence on the protection before membrane defects of cells with an elevated level of prelamina A of a wild type [5].

Last publications imply that there might be a relation between lamin A mutation and change of reactive oxygen species (ROS) metabolism. The researchers conducting the study noticed an increase in the number of ROS and increased sensitivity on oxidative stress in people who suffer from laminopathies caused by a defect in the *LMNA* gene such as Dunnigan-type familial partial lipodystrophy (FPLD) [6, 7], autosomal dominant Emery Dreifuss muscular dystrophy (AD-EDMD) [7, 8], Hutchinson-Gilford progeria syndrome (HGPS) [7, 9], restriction dermopathy (RD) [7, 9]. Free radicals such as peroxide, hydroxyl radicals, nitric oxide, oxygen radical, singlet oxygen damage cell membrane, cause modifications of nucleic bases, DNA single-strand breaks, exchange of sister chromosomes, cross-linking between DNA and protein, modification of carbon in proteins, racemization of amino acids, non-enzymatic glycosylation of proteins and loss of sulfhydryl groups in proteins. Oxidative stress induces nuclear factor (NF-κB), which is a transcription factor and causes inflammation. Singlet oxygen activates matrix metalloproteinases (MMP), but inactivates their inhibitors which cause damage to collagen. Reactive oxygen species are formed during oxygen metabolism, inflammation, reaction to ultraviolet (UV) radiation. A mitochondrial respiration chain is a fundamental source of ROS. The potential of mitochondrial membrane is decreased with age, but formation of ROS rises in the cell. Oxidative stress causes mutation of mitochondrial DNA and may accelerate telomere shortening [10].

Farnesylated prelamina A causes formation of ROS and oxidation of proteins [7, 9, 10]. Oxidized proteins are degraded in proteasome. Along with age aggre-

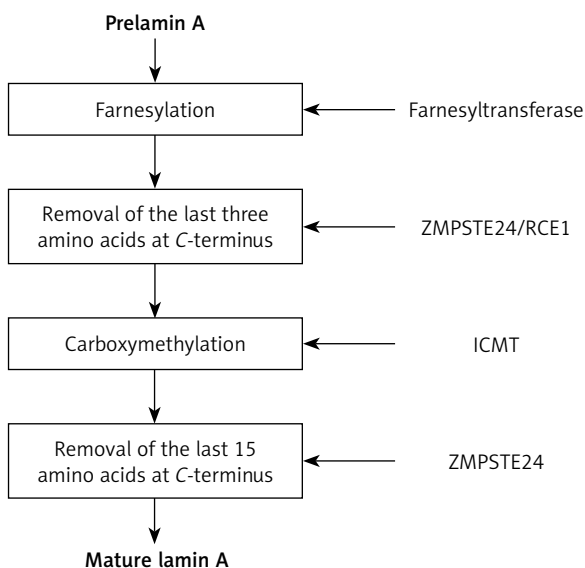


Fig. 1. Posttranslational modification of prelamina A

gates of oxidized proteins, which cannot be digested are formed. That results in accumulation of lipofuscin which inhibits the action of proteasome of fibroblasts and leads to accumulation of mutant form such as progerin. Generation of ROS induced by UV activates receptors for epidermal growth factor (EGF), interleukin 1 (IL-1), insulin, factor of keratinocyte growth (KGF), tumor necrosis factor (TNF- $\alpha$ ). That causes transduction signal through mitogen-activated protein kinase (MAPK). Ultraviolet inhibits a phosphatase and tensin homolog (PTEN) and activates serine-threonine protein kinase (Akt), which is the main messenger in P13 pathway and plays an important role in regulation of processes connected with growth, metabolism, survival and proliferation of cell. Activator protein (AP-1) causes a formation of the photoaging phenotype. Activation of metalloproteinases leads to a decrease in the amount of collagen and stops the function of TGF- $\beta$ . Inhibition of TGF- $\beta$  and induction of SMAD7, a protein which binds ubiquitin ligase SMURF2 contributes to an increased keratinocyte proliferation. Degradation of lipids caused by UV induces inflammation, release of arachidonic acid, which is next converted to prostaglandins [7].

Decrease in the level of mature lamin A and presence of changed isoforms of prelamin influence the level of antioxidant proteins. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GTP), thioredoxin 1, vitamin E, coenzyme Q10, vitamin C and carotenoids take part in antioxidant defense. Reduced quantity of CAT, GPX was detected in fibroblasts derived/isolated from a person with HGPS [7, 11]. An increased level of SOD, CAT, and GST was detected in fibroblasts which were lacking in lamin [7, 8, 12].

Reactive oxygen species action contributes to protein oxidation, telomere shortening, and DNA damage [7, 13]. Telomere shortening leads to an early cell cycle arrest, because of activation of tumor suppressor p53, which suppresses PGC-1 $\alpha$  and PGC-1 $\beta$ , i.e. regulators of mitochondrial processes. Dysfunctional lamin may be a result of mutation of genes which encode lamins and other proteins involved in maturation of prelamin A. Moreover, dysfunction of lamins may be an effect of treatment with HIV antiviral protease inhibitor (HIV-PIs), whose side effect includes blocked Zmpste24 or irreversible damage to mature lamins [7, 8]. Accumulation of farnesylated prelamin A in cells contributes to a decrease in the expression of mitochondrial DNA (mtDNA), which is encoded by the second subunit of cytochrome oxidase in IV complex of the respiration chain (COX2). It disrupts electron transport in the respiration chain and causes changes in ATP generation and reactive oxygen species [7, 10].

Immunofluorescent analysis of the primary dermal fibroblast cell line showed an elevated growth of the expression of prelamin A of wild type and influence on formation of aggregates of lamin A. Such structures are

observed not only in ill cells, but also in cells derived from old people. Distribution of lamin A in the cells is diversified. In cells with farnesylated prelamin A variants, a growth of folded lamin A aggregates was observed. In contrast, prelamin A which was not farnesylated, appears as nucleoplasmic foci. Fluorescent microscopic examination showed folded structures of lamin A, which were situated in NE and could penetrate to nucleoplasmic regions. The foci of lamin A were located between nucleoplasm. Hutchinson-Gilford progeria syndrome cells and cells with an elevated prelamin A of wild type are characterized by changes in nuclear membrane morphology because of blebs [14]. Expression of truncated forms of lamin A mutant influences RNA synthesis. In order to check the influence of prelamin A on transcription an experiment was performed which included making measurements of the level of transcription in fibroblast culture. The measurement was made with the application of radioactive labeled uridine, penetrating into RNA chains. A result of the measurement was a decrease in the transcription level of prelamin A'L647R (in 647 position of protein was arginine except leucine), which cannot be cleaved by ZMPSTE24 ( $n = 3$ ,  $p = 0.005$ ). Also the level of TATA-binding protein (TBP) appeared to get reduced in those cells [5].

### Progerin in skin aging

Progeria is a good example for studying reasons for human physiological aging. In professional literature the process of skin aging is analyzed on the basis of HGPS, which affects one baby per 4 million births. Hutchinson-Gilford progeria syndrome is a genetic disease which is inherited dominantly. Symptoms of the disease appear in the first months of life and they include accelerated aging, delayed growth, loss of subcutaneous fat, baldness, decreased density of bone, and weak muscles. People affected by the diseases die when they are about 15 years old and the most common reason is myocardial infarction [15].

Studies performed by Scaffidi and Misteli revealed that lamins A/C are involved in aging [16]. The mechanism of HGPS is caused by a point mutation, which is an exchange of cytosine to thymine in 1824 position of 11 exon in *LMNA* gene. In that case, lamin A is 50 amino acids shorter at C-terminus of globular domain [15] and it is not hydrolyzed by metalloprotease dependent on zinc ions (ZMPSTE24), because of changed sequence at C-terminus [3, 17]. That protein is called progerin (LA $\Delta$ 50). In the healthy cells a level of expression of short lamin A is connected with age. Changes which appear in the cell nucleus of old people are similar to those in people with HGPS. They most often apply to DNA damage, histone modification, protein import to nucleus [3]. It was revealed that progerin accumulates in the skin, tongue, thorax, heart, liver, kidney, stomach, bladder, pancreas,

spleen, thyroid, adipose tissue, arteries, bones, and skeletal muscles. Progerin affects the organization of chromosomes by changing the distribution and level of heterochromatin, as well as it causes telomere shortening. Such cells are hyperproliferated and this results in apoptosis [18]. Cao *et al.* [18] proved that telomere damage in fibroblasts of healthy people activates progerin production and that implies an influence of telomere dysfunction on cells aging and expression of progerin. Telomeres are specialized structures located at the ends of chromosomes and they are composed of DNA repeats. They protect chromosomes before degradation, are not copied by DNA polymerase and are elongated by ribonucleoprotein called telomerase. Telomerase expression is independent of age and regulated by sexual hormones. Benson *et al.* [18, 19] revealed that progerin expression in human diploid fibroblasts causes telomere aggregation, telomere DNA damage and chromosome aberrations. They revealed that progerin rapidly induces telomeres dysfunction and that leads to appearing of serious DNA damages in cell structures. Influence of progerin on telomeres does not depend on telomere DNA shortening. Repairs of telomeres are slower than in case of other DNA sequences. Telomerase is dysregulated in the skin exposed to sun light, which might result in photocarcinogenesis. One of hypotheses is that proteins of "Shelterin" complex such as TRF1, TRF2, POT1, TIN2, Rap1, TPP1 are released from telomere ends during shortening or damaging. In the fibroblasts culture aging dependent on p53 was an answer to difficulties with repairing of DNA damage [7, 13, 20]. An alternative splicing influences cytoskeleton reorganization during aging. Previous studies revealed that fibronectin and vimentin undergo alternative splicing in aging cells. An activity of heterogeneous nuclear ribonucleoproteins (hnRNPs) such as hnRNPA1 and hnRNPA2, which bind to RNA and single-stranded DNA, is reduced in aging cells. In the HGPS cells aging caused by the presence of progerin is partly connected with the activation of p53 and is a signal for the cell before apoptosis. That causes a relaxation of nuclear lamin area and decondensation of chromosomes and fragmentation of DNA. All these features cause cell dysfunction, decrease their lifespan and give rise to age-related pathologies [18].

Research conducted on skin fibroblasts cell lines derived from old people (81 to 96 years) showed nuclear defects dependent on lamin A. The level of histone H3 was reduced by about 40% to 90% in cells derived from old people. The percentage of reduced amount of heterochromatin protein HP1 and H3 in cells from old people was similar to that observed in HGPS cells. Similar differences were noted in proteins connected with lamin A, such as LAP2. Defects of nuclei of HGPS cells accumulate during culture. With regards to HGPS cells there is a lot of unrepaired DNA damage and this observation can be identified by presence of foci with phosphorylated histones H2AX [16].

The level of progerin mRNA in skin samples from healthy people (from newborns to 97-year-old patients) was low and a similar observation was noticed in fibroblasts isolated from healthy people. It was revealed that progerin is found in dermis fibroblasts and terminally differentiated keratinocytes. Furthermore, cells in which progerin is expressed are at first observed in the basal layer and then move upwards to the suprabasal layer. A lot of cells which contain progerin were detected in skin biopsies from old people, whereas a few of them were found in the suitable phase of fibroblasts culture growth. Thus, it can be concluded that progerin accumulates in keratinocytes or senescent cells. The epidermis is built of keratinocytes, which are terminally differentiated during life. This process begins in the basal layer and proceeds to the upper compartment of the skin. Terminally differentiated keratinocytes of the granular layer are a transitional phase to form the cornified layer of the epidermis and the process results in a removal of the nucleus and changes of cytoplasm functioning. That causes a production of corneocytes, which make up a skin barrier. This process needs changes of heterochromatin to silence gene expression and causes terminal differentiation of these cells [21].

### Inhibition of skin aging

Progerin expression leads to changes in the function and shape of the nucleus in cells of HGPS syndrome but also in normal cells. Intrinsic aging is often different from photoaging. Changes that occur during intrinsic aging are similar to those caused by photoaging, but there are additional effects caused by exposure to sunlight. An effect of photoaging is seen in all levels of the skin such as the epidermis, dermis, pigmentation, and vascular system and it is often accompanied by an increased risk of skin cancer. Ultraviolet A (UVA) radiation (315-400 nm) rather than ultraviolet B (UVB) radiation (280-315 nm) reaches deeper layers of the skin (dermis). Ultraviolet B waves reach layers of the dermis which are higher located, as well as cause changes in the transmission of signals between epidermis and dermis. Solar activity might accelerate processes that do not occur during intracellular aging. A primary human fibroblasts culture was irradiated with UVA waves during studies. After the irradiation with a single and a strong dose of UVA it was found that the light had caused an increase in the level of progerin. Ultraviolet B radiation is not a factor which causes the expression of progerin. The induction of progerin in fibroblasts from 50-year-old donors was higher than from 77-year-old donors. Immunocytochemistry analyses were performed to illustrate a level of formed progerin compared to HGPS cells after repeated exposure to UVA radiation. Research data indicate that UVA induces progerin by alternative splicing of the *LMNA* gene transcript. Previous results showed

that a short UVC ultraviolet radiation causes the alternative splicing of genes involved in apoptosis and cell proliferation [22].

Aesthetic medicine uses laser treatments, microdermabrasion, mesotherapy, chemical peelings, radio-frequency, iontophoresis, cryotherapy and other surgical methods. There are many substances which contain biomimetic peptides on the market. Biomimetic peptides, which are organic compounds, are similar to their natural analogues (present in a body). They stimulate physiological processes in the skin, activate natural growth factors and synthesis of collagen, hyaluronic acid etc.

Elafin/SKALP (Skin Derived Antileukoproteinase) is an antileukoproteinase built of a transglutaminase domain at the *N*-terminus and a protease inhibitor domain at the *C*-terminus [23]. This protein is encoded by a trappin gene family. Trappin is an acronym for TRansglutaminase substrate and WAP domain containing ProteIN [24]. The *N*-terminus domain of elafin binds to laminin,  $\beta$ -crystallin, fibronectin which are extracellular matrix proteins and to some extent to collagen IV. SKALP/Elafin is a proteinase inhibitor and it is present in the epidermis of psoriasis as a short polypeptide with a mass of 6 kDa. The mature protein isolated from cultured human keratinocytes has a mass of 9.9 kDa and contains about 22 amino acids. So far an expression of elafin was detected in epidermis. During inflammation keratinocytes are hyperproliferated and that results in the expression of cytokeratins CK6, CK16, CK17 and elafin. It was revealed that an exposure of normal human skin to UVB radiation induces the expression of elafin and phosphorylation of c-jun and p-38. This inhibitor is found in epidermal cells in certain inflammatory diseases, but it is absent in normal cells. During the terminal differentiation of keratinocytes in the epidermis, the protein layer which is 15 nm thick is exposed to the interior surface of the cell. Nuclear envelope acts as a barrier for tissue. Potential nuclear envelope components include: involucrin, cystatin- $\alpha$  (5%), small proline-rich proteins (SPR1, SPR2, SPR3) (5%), loricrin (70%), keratin intermediate filaments (2%), filaggrin (8%), cysteine-rich proteins such as elafin (approximately 6%) [25]. They cross-link through disulfide bonds, as well as isodipeptide *N*-( $\gamma$ -glutamic) lysine, which arise due to the activity of epidermal transglutaminases. Elafin contains a lot of transglutaminase substrate domains and is a component of the cornified envelope of the epidermis. It also contains a signal peptide sequence. Elafin presence in platelet granules and the intracellular space were identified by immunoelectron microscopy. In the healthy epidermis secretion of granule content finishes before keratosis. In the epidermis of psoriasis the nuclear envelope was prematurely created in the stratum spinosum. It was shown that an increase in intracellular calcium ions concentration occurs in terminally differentiated keratinocytes. Moreover, it leads

to exocytosis of the Golgi apparatus and cross-linking of proteins by transglutaminase. Calcium ions induce nuclear envelope formation, accompanied by the activation of transglutaminase 1 in normal human keratinocytes. That means that, until the increase in the level of calcium ions, the released elafin is located between the granules, nuclear envelope is created, and secretory granules are not capable of disintegrating [22].

Biological functions of elafin influence cell proliferation, inflammation and infection. Elafin-elastin complex protects elastic fibers before degradation and contributes to their accumulation if the skin has been damaged by UV radiation, osmotic stress or inflammatory cytokines. In solar elastosis histopathological changes occur in elastic fibers of the dermis and are separated from the epidermis with a thin layer of collagen. Disorders of the synthesis of fibrillin, which is responsible for a right cross-linking of elastin fibers, are main factors contributing to the occurrence of solar elastosis. Some anti-aging cosmetic products are composed of synthetic tripeptide which resembles the activity of elafin.

## Conclusions

Progerin is one of biomarkers, which is used in studies on natural aging. This protein is expressed as a mutant form of the *LMNA* gene. Because of that it causes many defects in the area of the nuclear envelope. It also influences a level of reactive oxygen species and antioxidant enzymes. It decreases the activity of proteasomes, causes epigenetic changes, problems with regulation of replication and transcription. That leads to cell dysfunction, apoptosis and results in senescence of organism. Many studies were performed to understand the mechanism of aging processes which is similar to the mechanism of Hutchinson-Gilford progeria syndrome. It is a genetically conditioned disease, which accelerates aging and leads to death at about 15 years of life. A search for an effective way to fight the disease is still a big challenge. Cosmetologists use many solutions to fight symptoms of skin aging. Moreover, it is also important to lead a healthy lifestyle.

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