

Epigenetic Involvement in Hutchinson-Gilford Progeria Syndrome: A Mini-Review

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Abstract

Hutchinson-Gilford progeria syndrome (HGPS) is a rare human genetic disease that leads to a severe premature ageing phenotype, caused by mutations in the *LMNA* gene. The *LMNA* gene codes for lamin-A and lamin-C proteins, which are structural components of the nuclear lamina. HGPS is usually caused by a de novo *C1824T* mutation that leads to the accumulation of a dominant negative form of lamin-A called progerin. Progerin also accumulates physiologically in normal ageing cells as a rare splicing form of lamin-A transcripts. From this perspective, HGPS cells seem to be good candidates for the study of the physiological mechanisms of ageing. Progerin accumulation leads to faster cellular senescence, stem cell depletion and the progeroid phenotype. Tissues of mesodermic origin are especially affected by HGPS. HGPS patients usually have a bad quality of life and, with current treatments, their life expectancy does not exceed their second decade at best. Though progerin can be expressed in almost any tissue, when death occurs, it is usually due to cardiovascular complications. In HGPS, severe epigenetic alterations have been reported. Histone-covalent

modifications are radically different from control specimens, with the tendency to lose the bipartition into euchromatin and heterochromatin. This is reflected in an altered spatial compartmentalization and conformation of chromatin within the nucleus. Moreover, it seems that microRNAs and microRNA biosynthesis might play a role in HGPS. Exemplary in this connection is the suggested protective effect of miR-9 on the central nervous system of affected individuals. This mini-review will report on the state of the art of HGPS epigenetics, and there will be a discussion of how epigenetic alterations in HGPS cells can alter the cellular metabolism and lead to the systemic syndrome. © 2014 S. Karger AG, Basel

Hutchinson-Gilford Progeria Syndrome

Progeroid syndromes are a group of systemic diseases that greatly resemble physiological ageing. Indeed, the term 'progeria' means 'prematurely old'. They usually refer to segmental progerias, where multiple tissues and organs are affected and patients usually show only some of the phenotypes and clinical conditions associated with ageing. They are all monogenic disorders that somehow alter either one of the DNA repair mechanisms or components of the nuclear lamina.

Hutchinson-Gilford progeria syndrome (HGPS) was named after Dr. Jonathan Hutchinson and Dr. Hastings Gilford, who first described it in England 1886 and 1897, respectively. It is a very rare disease, reported to occur in 1 in 8 million newborns worldwide. More than 130 cases have been reported in the scientific literature since the condition was first described [1].

HGPS phenotypes greatly resemble those that occur during natural ageing. One of the most striking differences is that HGPS is considered a developmental disease, as there is an improper development of tissues, especially of those of mesenchymal origin, before the development is complete [1].

HGPS is characterized by severe alterations of the nuclear architecture. Experimental data strongly suggest that these alterations may have a deep impact on the epigenetic state of the chromatin and in the regulation of transcription. Interestingly, the epigenetics of HGPS often resemble the epigenetics of normal ageing. It is still a matter of debate if and to what extent progeroid syndromes, especially HGPS, can be used as models of physiological ageing.

HGPS is a genetic condition characterized by the dramatic, rapid appearance of ageing beginning in childhood. Affected children typically look normal at birth and in early infancy, but then grow more slowly than unaffected children and experience what is commonly known as a 'failure to thrive.' They develop a typical facial appearance including prominent eyes, a thin nose with a beaked tip, thin lips, a small chin and protruding ears. Patients with HGPS also have complete alopecia, aged-looking skin, joint abnormalities and loss of subcutaneous fat. The condition does not disturb the intellectual development or the development of motor skills.

People with HGPS experience severe arteriosclerosis beginning in childhood. This condition greatly increases the chances of having a heart attack or stroke at a young age. These serious complications can worsen over time and are life-threatening. Children with HGPS typically die of heart disease at an average age of 13 years. HGPS is an autosomal dominant condition caused by de novo mutations in the *LMNA* gene that codes for nuclear lamins [1].

Lamins are nuclear intermediate filaments with structural and regulative functions, present in all metazoans. The absence of lamins in unicellular organisms is worth noting. Four major lamins are present in humans: lamin-B1 and lamin-B2, coded from two independent loci, and lamin-A and lamin-C, coded by the same *LMNA* gene by alternative splicing.

Mutations in nuclear lamins cause a very heterogeneous class of diseases called laminopathies. The accu-

mulation of a particular splicing form of lamin-A, called progerin, leads to the rare HGPS laminopathy. For an exhaustive review on lamins, please refer to Dechat et al. [2].

Usually, lamin-A is synthesized as a precursor of the mature form. The C-terminus of the protein undergoes multistep posttranslational processing. On its C-terminal CaaX motif, the precursor is farnesylated on cysteine, and then the remaining 3 amino acids are cleaved. The C-terminal cysteine is then carboxymethylated. The farnesylated and carboxymethylated pre-lamin-A is then anchored into the inner nuclear membrane. Finally, the last 18 amino acids are cleaved by the metallopeptidase Zmpste24 to produce the mature, unfarnesylated lamin-A.

In HGPS, the proper synthesis and maturation of lamin-A is impaired. This is usually caused by a de novo autosomal dominant synonymous G608G mutation within exon 11 of the *LMNA* gene (*C1824T* at the nucleotide level). This mutation activates a cryptic splicing site that leads to the production of a protein, called progerin, lacking 50 amino acids. This deletion abrogates the ZmpSte24 cleavage site, so progerin becomes constitutively farnesylated and anchored into the inner nuclear membrane [2].

A- and B-type lamins are expressed differently during differentiation. B-type lamins seem to be essential and ubiquitously expressed. By contrast, lamin-A production begins during differentiation and is maintained in fully differentiated cells [3]. It is to be noted that progerin seems to physiologically accumulate in cells as a function of the chronological age of donors and the number(s) of passages in culture. Progerin in nonmutated individuals is produced as a rare splicing form using a cryptic splicing site. Cells that accumulate progerin are prone to senescence, and animal models of HGPS recapitulate the progeroid characteristics of HGPS. From this perspective, HGPS cells are very good candidates for studying the physiological characteristics of human ageing. Interestingly, induced pluripotent stem cells from individuals affected by HGPS or from very old people are indistinguishable from those obtained from healthy donors. Intriguingly, as has been noted for embryonic stem cells, reprogrammed induced pluripotent stem cells do not express lamin-A [4]. This gives rise to the possibility that abrogating lamin-A expression may serve to treat both HGPS and physiological ageing.

At the cellular level, lamins can directly and indirectly bind to DNA in matrix attachment/scaffold-associated regions, though clear consensus sequences do not seem to be present. Lamin-associated regions tend to be heterochromatic and transcriptionally silent [5].

HGPS causes typical cellular phenotypes such as nuclear lobulation or blebbing – the cytological hallmark of

HGPS – mitochondrial dysfunction [6], increased reactive oxygen species production [6] and chromosomal and telomere aberrations [7]. HGPS cells have altered cell-cycle regulation, impaired DNA repair mechanisms, a higher apoptosis rate and quicker cellular senescence [7].

The alteration of the cell cycle seems of particular interest; indeed, it has long been known that retinoblastoma protein is stabilized and regulated by nuclear lamina interactions [8]. Hence, the altered cell-cycle regulation observed in HGPS cells is probably due to an impaired function of the retinoblastoma protein network. Moreover, two recent *in silico* ceRNA and interactome analyses [9, 10] pointed to several other genes involved in the control of the cell cycle (*TP53*, *MYC* and *E2F1* amongst many others) that might be deregulated in HGPS, but the significance of this is still to be investigated. Unexpectedly, the occurrence of cancer in HGPS patients is a very rare event [1, 3]. This is one of the major differences between the HGPS phenotype and physiological ageing.

In HGPS, severe epigenetic alterations have been reported. Histone-covalent modifications, histone variants, DNA methylation, chromatin remodelers, chromatin architecture and miRNAs are all altered in HGPS. The epigenetic changes reported in HGPS and how these might lead to the cellular phenotype will be discussed in detail in this mini-review.

Histone Modifications

Profound alterations in the histone-covalent modifications of HGPS cells have been widely reported. These alterations concern both the type and spatial localization of the modification. Usually, nuclear lamina constitutes a repressive heterochromatic environment for the chromatin territories associated with it. In HGPS, there is a loss of peripheral heterochromatin and relative histone modifications (H3K9me3, H3K27me3) and associated proteins (HP1).

H3K9me3 is one of the constitutive heterochromatin markers of the pericentric region and telomeres. It is downregulated in HGPS, and pericentric regions tend to be less associated with the nuclear lamina. As a consequence, pericentric transcription arises and the association with HP1, which recognizes H3K9me3, decreases [2, 11].

H3K27me3 is another heterochromatic marker that marks, for example, the X-inactive chromosome in humans. In HGPS, it is downregulated, just like the H3K27 methyltransferase EZH2 [11].

The opposite behavior is shown for H4K20me3, which is upregulated in HGPS cells. Interestingly, it marks telomeric heterochromatin, and an increase in H4K20me3 blocks telomere elongation. The data are consistent with the reported telomere dysfunction and accelerated senescence in HGPS cells [12]. H4K20 monomethylation also seems to increase in HGPS cells and acts as a marker of transcriptionally active chromatin [11, 13].

A detailed epigenome mapping analysis has revealed that there is a trend towards homogeneous redistribution of epigenetic markers in HGPS cells. As a consequence, the difference between high-expression genes and low-expression genes tends to be minimized. Exemplary in this connection is H3K27me3 (as a marker of facultative heterochromatin). Though it is downregulated as an absolute quantity in HGPS cells compared with control cells, the remnant H3K27me3 is widely redistributed within HGPS chromatin. The trend reported is that H3K27me3 decreases in gene-poor regions and increases in gene-rich regions. This correlates with the increased expression of poorly expressed genes and the decreased expression of highly expressed genes [14]. Interestingly, the same trend has been reported in senescent cells.

The data on histone methylation are quite robust; the role of acetylation in HGPS, however, is still controversial. Sirtuins are deacetylases that are also active on acetylated histone substrates, with a suggested role in regulating ageing processes. SIRT1 deacetylase activity is greatly enhanced by lamin-A association and is downregulated in senescent cells. Reported targets of SIRT1 are H4K16ac and H3K9ac. Consistently during ageing, H4K16ac is upregulated [15]. Opposite data have been retrieved in an HGPS mouse model, however, where histone H4K16 hypoacetylation was associated with premature senescence that might have been reversed by a histone acetyl transferase (HAT) Mof overexpression or by histone deacetylase inhibition [16]. Interestingly, in a recent *in silico* interactome analysis, a central role of histone acetylation has been proposed for the *LMNA* network, with a bias toward the histone deacetylase *HTATIP* (also known as *KAT5* or *TIP60*), which is the catalytic subunit of the NuA4 histone acetyltransferase complex that preferably targets H2A and H4 histones [10].

Apart from methylation and acetylation, other histone-covalent modifications seem to be altered in HGPS. *PARP1* [the poly (ADP-ribose) polymerase 1 gene] is a gene that has been linked to longevity in mammals [17]. *PARP1* has a key role in regulating cell-cycle and DNA repair mechanisms. Moreover, histones and other chromatin proteins are the *PARP1* substrates of choice. Interestingly, *PARP1* is downregulated in HGPS cells [18].

Histone sumoylation also seems to be reduced in HGPS, with severe consequences in heterochromatin formation. Indeed, an increase in progerin is correlated to a reduced ratio between the nuclear and cytoplasmic Ran GTPase. This, in turn, inhibits the nuclear localization of Ubc9, the only known E2 required for sumoylation. Interestingly, usually both histones and chromatin remodelers tend to be deeply sumoylated [19]. Reduced sumoylation of histones and other nuclear proteins may be expected in HGPS cells.

Histone Variants

Histones are a major component of chromatin, fundamental to genome regulation. Histone variants lead to changes in chromatin dynamics and carry out specific functions. In addition, posttranslational modifications that occur on the variants may be different from those of canonical histones. Histone variants differ mostly in the N-terminal region from their canonical counterpart. More than 50 unique histone variants are present in humans. The expression of histone variants can be replication dependent or replication independent. Histone variants can mark a specific region of the DNA by replacing canonical histones. It has been suggested that histone variant retention could be involved in epigenetic cellular memory.

In HGPS cells, a 6-fold downregulation of the mRNA for the H2A.X histone variant has been reported, often associated with a region of damaged DNA and a 2-fold downregulation of the mRNA for centromere-specific chromobox homolog 1 (CBX1) [18]. These data are consistent with the reported altered DNA repair mechanisms and centromere dynamics. It is interesting that HGPS cells are characterized by many unrepaired DNA double-strand-break γ H2A.X foci (marked by phosphorylated H2A.X) [20]; this poses interesting questions about the increased demand for and the decreased availability of H2A.X in HGPS cells. Of note, the accumulation of unrepaired DNA damage leads to the activation of ATM and ATR checkpoint kinases and cell-cycle arrest. It has been suggested that the accumulation of γ H2A.X foci might be due to the lack of activity of the NuRD complex. The most striking characteristic of DNA damage-response impairment in HGPS cells is that γ H2A.X foci fail to recruit Rad50 and Rad51 and instead recruit the Xeroderma pigmentosum group A protein (XPA), involved in the excision repair mechanism. It seems that the recruitment of XPA instead of Rad50 and Rad51 causes the failure of the double-strand-break repair mechanism [20]. This is a

very rare, if not unique, example of a DNA repair mechanism that seems to impair the function of another.

An *in silico* ceRNA analysis also pointed to the involvement of the poorly studied H2AFY2 macroH2A histone variant [10]; a protective role in tumorigenesis and a role in ageing and X inactivation in mammals have been suggested for H2AFY2.

Interestingly, differences in the expression of core histones have also been reported. A proteomic study [21] showed a profound downregulation of histone H4 in HGPS cells compared to control cells. This poses an interesting and unanswered question on the composition of nucleosomes in HGPS cells lacking H4 core histones. Moreover, the same study [21] pointed to the downregulation of histone H2B types 2-E, 1-M and 1-C/E/F/G/I in HGPS, which is of unknown biological significance.

DNA Methylation

Cytosine methylation on CpG islands on gene promoters is often involved in transcriptional silencing. In HGPS, the methylation profile is perturbed.

In a mouse model of HGPS, ribosomal RNA genes (rDNA) are hypermethylated. The same phenotype can be observed in ageing mice. The production of ribosomal RNA is consistently downregulated [22].

More recently, it has been observed that CpG sites in HGPS cells gain methylation when compared to hypomethylated control regions but lose methylation when compared to hypermethylated control regions [23]. Again, the trend is a homogeneous redistribution of epigenetic markers in HGPS specimens.

ATP-Dependent Chromatin Remodelers

ATP-dependent chromatin remodelers usually act in huge multiprotein complexes. The complexes are organized around a protein with ATPase activity. The energy from the hydrolysis of ATP allows these remodeling complexes to change the relative positioning of nucleosomes on the DNA string, to expel or exchange histones or to alter the local chromatin topology.

Specifically, a role for the NuRD complex has been proposed in HGPS. NuRD is a chromatin-remodeling complex with both ATP-dependent chromatin-remodeling and histone-deacetylase activities. Progerin lacks the amino-acidic sequence required to contact RBBP4/7 of the NuRD complex and, in turn, the NuRD complex ac-

tivity seems to be impaired. Moreover, the interaction between lamin-A and NuRD is required to maintain a correct H3K9 methylation profile and the correct loading of heterochromatin protein 1 gamma (HP1 γ) in chromatin. It has been suggested that these alterations might be the cause of the reported reduction in NuRD functions within a nuclear lamina context and the loss of peripheral heterochromatin in HGPS cells [24].

In addition, *in silico* analyses looking for attributes relevant to gene ontology in the *LMNA* network have pointed to the potential involvement of ATP-dependent chromatin remodelers. A more detailed analysis has revealed a bias towards the *SMARCA4* (also known as *BRG1*), *PBRM1* and *SMARCB1* genes and pBAF and SWI/SNF complexes [10].

Nuclear Architecture

Chromosomes are nonrandomly organized into chromosomal territories. Gene-poor heterochromatic regions are preferably located closer to the nuclear lamina. Transcriptionally silent chromatin is usually in the interior of chromosomal territories, while transcriptionally active chromatin is located on the surface [2, 5, 7]. The nucleus is like a worm-eaten apple where the transcriptionally active euchromatin tends to be located towards the worm-holes. In HGPS, the nuclear organization and the relative epigenetic markers are subverted.

In HGPS, the nuclear lamina is highly disorganized. Typically, progerin accumulation provokes a severe distortion of the nuclear lamina with typical blebbing that can be cytologically observed. This distortion of the lamina is associated with a severe loss of nuclear organization and nuclear compartmentalization [2, 5, 7]. It seems that the nuclear lamina is required for the correct organization of heterochromatin in the nuclear periphery. The accumulation of progerin strongly interferes with the metabolism of peripheral heterochromatin as well as with the whole nuclear architecture and heterochromatin/euchromatin spatial bipartition [14]. Indeed, in HGPS, there is a clear loss of peripheral heterochromatin and relative histone modifications (H3K9me₃, H3K27me₃) and associated proteins (HP1) [25]. In fact, heterochromatin tends to dissociate from the nuclear lamina, and there is a loss of spatial nuclear compartmentalization [14].

Several genes involved in the maintenance of the nuclear architecture are altered in HGPS. The cellular distribution of barrier-to-autointegration factor (BAF), a mitotic heterochromatin organization factor associated

with the nuclear lamina, is profoundly altered in HGPS. Usually, BAF is present at both the nuclear and cytoplasmic levels, but in HGPS the cytoplasmic pool is severely depleted [26]. Interestingly, it has been reported that a mutation in BAF coded by the *BANF1* gene leads to a progeroid phenotype [27].

In HGPS cells, the expression, function and nuclear localization of inhibitor of growth protein 1 (ING1) are impaired. ING1 is a tumor suppressor of the p53 pathway with a reported role in apoptosis and senescence. It usually has a bridge function between a methylated histone H3 and the acetylase/deacetylase complexes, and it is involved in the formation of peripheral heterochromatin [28].

The D4Z4 human subtelomeric repeats localize the telomeres to the nuclear periphery in a lamin-A-dependent manner [29]. This function is probably altered in HGPS.

High mobility group (HMG) proteins are able to bind and bend DNA double strands. The transcription of HMG-B2, HMG-17 and HMG-2 proteins is downregulated in HGPS cells [18]. The transcription of heterochromatic CBX1, also known as heterochromatin protein 1 homolog beta, is downregulated in HGPS cells [18]. It is a heterochromatic protein that recognizes and binds H3K9me₃, leading to epigenetic repression. It contributes to the association of heterochromatin with the inner nuclear membrane.

In silico analyses have also pointed to the involvement of *CBX5*, which codes for HP1 α , a heterochromatic protein that recognizes and binds H3K9me₃, leading to epigenetic repression [10].

miRNAs

miRNAs have multiple roles in negative and possibly in positive gene regulation. This regulation may be asserted at the transcriptional, posttranscriptional and translational levels. miRNAs are involved in most biological processes. The aberrant expression of miRNAs has been implicated in numerous pathological states.

Amongst the miRNAs, an important role for miR-9 has been suggested in HGPS. miR-9 is the only validated miRNA that interacts with the 3' UTR of lamin-A/progerin mRNA, and it plays a clear neuroprotective role in the brain. Lamin-A and progerin have the same 3' UTR, but lamin-A and lamin-C have different 3' UTRs. In a mouse model, it seems that the brain-specific miR-9 is able to strongly downregulate the production of lamin-A/progerin, leaving the level of lamin-C unchanged, via the inter-

action with lamin-A/progerin 3' UTRs. This might explain why the mouse models of HGPS are free of central nervous system pathology. A similar mechanism of protection could be hypothesized for humans, also with no involvement of the nervous system of HGPS patients [30].

Some interest has arisen about the miR-29 family. Indeed, in a mouse model of HGPS, the tumor suppressor miR-29 family is upregulated in response to DNA damage in a p53-dependent manner [31]. The authors of that study suggested that miR-29 may act as an ageing promoter, as many classic oncogenes are reported to be.

Interestingly, Arancio et al. [9] suggested a role for Dicer1, Argonaute1, Argonaute2 and Drosha (which have key activities in miRNA metabolism) and, to a lesser degree, Pasha (a partner of Drosha) in the lamin-A/progerin network.

Unanswered Questions

There are still many questions that are waiting for an answer. The first is whether studies on HGPS might help to ameliorate the conditions of elderly people. There is an ongoing debate about the evolutionary ageing hypotheses [32] and on how HGPS could play a part here. Another question is whether or not HGPS studies might help to uncover the mechanism of ageing in order to slow it down, stop it or even reverse it. It is clear that in HGPS cells, the epigenetics are profoundly altered, and many efforts have been made to elucidate the changes in the patterns of histone methylation. Unanswered questions remain concerning the dynamics of histone acetylation. Many studies have pointed to a central role of acetylation/deacetylation patterns and related modifying complexes in HGPS chromatin, but the data are not exhaustive and often controversial.

Interestingly, the reported downregulation of *PARP1* and histone H4 might have a deep impact on chromatin dynamics, but there are almost no data on their role in HGPS.

Intriguingly, the downregulation of Hsp90 in HGPS cells has been reported [21] and a role for Hsp90 in the inhibition of mutagenic activity of endogenous retrotransposons has been demonstrated [33]. In the authors' opinion, these data taken together suggest a possible contribution of the reactivation of formally dormant transposable elements on the reported genomic instability in HGPS cells [20].

At least, the role of the histone variant H2A.X is interesting. In HGPS, it is downregulated, but it is very much

in demand in the attempt to repair putative multiple double-strand breaks at the level of γ H2A.X foci. Here, once again, the double-strand-break repair mechanism is impaired due to the presence of the proteins of the excision repair mechanism in the γ H2A.X foci. The biological significance of these events is not clear.

Future Perspectives

Experimental therapies rely on farnesylation inhibitors that turn progerin into a nonfarnesylated form that resembles the common lamin-A. Though these approaches seem to partially ameliorate the conditions of HGPS patients, an efficient cure is still to be developed.

Interestingly, in mouse models, it seems that only the expression of lamin-C, and not that of lamin-A, is compatible with life. The production of lamin-C only seems to occur physiologically in the mouse nervous system, thanks to the activity of miR-9 [30]. Strategies aimed at shifting the production from the *LMNA* gene towards lamin-C instead of lamin-A/progerin might soon be developed. A possible role of miR-9 in these strategies should be considered.

Conclusions

HGPS is a progeroid syndrome that seems to recapitulate many cellular and molecular characteristics of physiological ageing. How the accumulation of progerin leads to the phenotype is still under investigation. However, a clear change in the epigenetic landscape has been widely reported. In HGPS cells, there is a global loss of heterochromatic markers and an evident loss of asymmetry of epigenetic markers and levels of transcription amongst lowly and highly transcribed genes. This is associated with a partial loss of nuclear compartmentalization, which is probably due to the loss of the capacity of nuclear lamina to orchestrate the nuclear architecture via the involvement of the ATP-dependent chromatin remodeling complex NuRD amongst others.

At least there is increasing evidence of miRNA involvement in HGPS, and a suggested protective effect of miR-9 in the nervous system of affected individuals. A deeper understanding of how a disruption in the nuclear architecture could lead to such deep changes in chromatin dynamics and to an ageing phenotype might help to develop a healing strategy for progeroid syndromes and to ameliorate the condition of ageing humans.

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