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PROGERIA: AN ACCELERATED AGEING PROCESS.

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ABSTRACT

Ageing is not a programmed process, in the sense that no genes are known to have evolved specifically to cause damage and ageing. An emerging consensus is that ageing is a consequence of macromolecular damage by reactive oxygen species, which oxidize lipids, proteins and, in particular, DNA, with damage to the latter leading to mutations and chromosomal abnormalities. Some rare congenital diseases, Hutchinson–Gilford Progeria syndrome (HGPS), Werner's syndrome (WS) and Cockayne syndrome (CS) have attracted much interest, primarily because of their resemblance to an accelerated ageing process. Thus the mechanisms by which it takes place and the lamins which play a key role in maintaining cell and tissue integrity during ageing is the main part of the study. Thus, finding HGPS to be the result of pathogenesis rather than the result of true ageing may be exactly what we require for increasing understanding of the ageing process.

KEYWORDS

Hutchinson–Gilford Progeria syndrome, Werner's syndrome, macromolecular damage, lamins etc.

INTRODUCTION

Ageing and death are inevitable in the life cycles of organisms. An understanding of why we age and the processes underlying ageing has been a subject of much debate and research over the centuries. Within the past decade considerable progress has been made in determining which physiological processes influence longevity. An emerging consensus is that ageing is a consequence of macromolecular damage by reactive oxygen species, which oxidize lipids, proteins and, in particular, DNA, with damage to the latter leading to mutations and chromosomal abnormalities[1].

These changes cause the malfunction of cellular organelles, particularly mitochondria, resulting in cell and tissue degeneration. Neuroendocrine pathways, in particular the insulin/insulin-like growth factor (Ins/Igfr) pathway, are central to regulating longevity in multicellular animals and may well be significant in mammals[2]. The role of the Ins/Igfr pathway in regulating metabolism and longevity is also consistent with the observation that caloric restriction prolongs lifespan[3]. However, some rare congenital diseases, Hutchinson–Gilford Progeria syndrome (HGPS), Cockayne syndrome (CS) and Werner's syndrome (WS), have attracted much interest, primarily because of their resemblance to an accelerated ageing process.

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PROGERIA IN ANCIENT TIMES (early 19th century)

Progeria is defined by Mr. Hastings's Gilford as "primary spontaneous infantilism mingled with premature senility. The premature senility is its more obvious feature and only a few cases of it have been described. The patient, a boy weighing 6lb at birth (august 1911) was the first child of healthy parents he was fed at the breast for a time but was always puny and had a disproportionate large skull with prominent veins on it[4]. His mental faculties seem normal and he got on well with other children. Dr. J.C.Schippers first saw him in April 1915. He was a slightly built child with a very large rounded forehead, brown ill nourished skin, projecting eyes, bald and prominentlywind head, slightly enlarged thyroid and overlarge joints. The head was 49cm in circumference, the chest 48cm, and the child weighed 25lb. 18 months later the child was seen again, and was in much the same general condition. He was over 5 years of age but the anterior fontanel was still open, the head was 50 cm in circumference, the height was 88cm, the weight over 26lb and an Arneth blood count gave normal result.

Dr. J.C.Schippers mentions as the chief features of this case. Photographs, indirectly reproduced, show the build, pigmentation and aged look of the child; his faces recall that of the well known case recorded by Mr. Hasting's Gilford. Dr. J.C.Schippers discusses the pathogenesis of Progeria, which remains obscure.

PRESENT CASE OF PROGERIA IN INDIA

Progeria is a debilitating, rare illness and genetic disorder with just 45 odd cases in the world. The disease which infects one in four lakh people is present in India too. One of the family in Chhapra, Bihar; has seven children, of which five are Progeria patients.

Out Of the five, three daughters are dead; having passed away at the ages of 17, 24 and 13 respectively. Two sons are still alive, but their medical ages are 70 and 66 and two children are normal. The sad thing is that the villagers ostracized the Progeria-stricken family from Chhapra in 2003 because the children were considered bad omen. Father says "My children could not come out of the house in the day. They were considered bad omens; they were called ghosts and the villagers abused my wife as a witch. We had to make do on the periphery of the village". The legs of the children were really stiff at the delicate ages of 2 and 3"

This is the ONLY FAMILY in the world that has more than one case of Progeria (five to be precise). Though death is imminent, the children enjoy their lives and have fun. The children's suffer from osteo-arthritis and cannot bend their legs or sit properly. Their bodies are very weak and their liver and heart are under-developed. The longest lifespan for Progeria in the world is 23.

THE PROGERIAS

In the late 1800s, Hutchinson reported two young boys with 'congenital absence of hair and its appendages'. They, and an additional patient, were described further by Gilford, who proposed the term 'Progeria' for this condition[5]. HGPS is a rare developmental disorder affecting most of the organ systems in a manner that mimics, to some extent, features of natural ageing but at a markedly accelerated rate[6]. In fact, HGPS has been considered as a prototype of premature ageing syndromes. HGPS is thought to be a genetic disorder, yet the mode of inheritance, molecular basis and pathogenic mechanisms all remain elusive.

A second premature ageing disease is WS. In the majority of patients (83%), Werner's is inherited as an autosomal recessive disease due to mutations in WRN, a 30–50RecQ DNA helicase-exonuclease[7]. Unlike HGPS, WS is associated with an increased risk

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of neoplasms[8], although the mean age of death (47 years) in Werner's is much older than in HGPS, which possibly allows the accumulation of mutations that might enhance the risk of unchecked cell growth.

PROGEROID SYNDROMES AS A MODEL FOR HUMAN AGEING

Human segmental progeroid syndromes are monogenic diseases accelerating some, but not all of the features found in normal ageing[9]. Ageing is a complex multifactorial process, and progeroid syndromes provide useful models for ageing research (Table 1).

Causative genes can be studied, identifying processes potentially relevant to the mechanisms of ageing. The classic example is WS, caused by a mutation in a gene coding for a member of the RecQ helicase family[10]. The WRN helicase acts as a 'caretaker of the genome' functioning in both DNA repair and transcription, indicating that breakdown of these processes is important in promoting ageing. This implication is supported by the involvement of several progeroid disorders in genome maintenance and transcription.

The Cockayne syndrome B protein (CSB) defective in CS is a member of the chromatin remodeling family SWI/SNF. CSB has conserved helicase motifs, although so far it has not been reported to exhibit helicase activity. CS cells are defective in transcription coupled repair (TCR) and CS can be described as transcription and DNA repair deficiency syndrome[11].

HGPS is caused by mutations in Lamin A/C[12], encoding a nuclear envelope protein. Lamin A has been shown to affect RNA polymerase II transcription, probably mediated by alterations in chromatin organization[13].

Table .1

Some segmental progeroid disorders

Syndrome	Gene defect	Cellular processes affected	Mean life-span	Phenotype
Werner Syndrome[14, 15, 16, 17, 18, 20.]	Loss of function mutations in WRN, DNA Helicase.	Transcription, DNA repair(DSBR (HR and NHEJ), SSBR/BER), DNA recombination, DNA replication, Chromosomal aberrations, telomere metabolism, apoptosis	48 years	Graying of hair, skin atrophy, atherosclerosis, malignancies, diabetes mellitus, disorder of lipid metabolism, hypogonadism, autoimmunity, degenerative vascular disease, osteoporosis, cataracts, regional fibrosis
Cockayne Syndrome[11, 14, 15, 19, 20.]	Loss of function mutations in CSA and CSB, putative DNA helicase.	Transcription, apoptosis, DNA repair: NER(TCR), BER of some types of oxidative damage	20 years	Neurodegeneration, atherosclerosis, diabetes mellitus, disorder of lipid metabolism, hypogonadism, hypertension, osteoporosis, cataracts, regional fibrosis, deafness, thin hair, poor growth

Hutchinson Gilford progeria syndrome[15, 20.]	LMNA gene (Lamin A), Nuclear Envelope.	Nuclear stability and transcription	12 years	Atherosclerosis, sarcopenia, alopecia, sclerosis, osteolysis, reduced adipose tissue

HUTCHINSON–GILFORD PROGERIA SYNDROME (HGPS)

Patients suffering from HGPS display features normally associated with ageing such as graying of the hair, cardiovascular disease, muscle atrophy and skeletal abnormalities[21]. Diagnosis is typically made in childhood and progeria patients die of cardiovascular disease at a mean age of 12.7 years[22]. It is characteristic of the segmental nature of HGPS that there is no neurological affection. HGPS is caused by a dominant mutation in the LMNA gene encoding the structural nuclear protein lamin A/C[12, 23.] Disruptions in the nuclear lamina are likely to interfere with processes that require an intact lamina such as transcription, replication and organization of chromatin structure. Lamin A has been shown to affect RNA polymerase II transcription, probably mediated by alterations in chromatin organization. Table 2 contains a comprehensive, but not exhaustive list of symptoms commonly reported in the HGPS literature.

Table .2
Symptoms of Hutchinson–Gilford Progeria

Sr. No.	System or area	Symptoms
1.	Cartilage and bone	• Abnormal bone development and dysplasia • Thin cranial bones, open anterior fontanelle • Hypoplastic facial bones • Long bones have attenuated cortices, thin diaphyses, widened metaphyses, and • Premature fusion of epiphyses • Prominent, stiff joints with contractures in the skull, thorax, long bones and phalanges • Pyriform thorax; short, osteolytic, clavicles
2.	Facies and related	• Prominent scalp veins visible through the skin • Prominent, owl-like eyes • Beaked nose with sculpted tip • Small mouth with thin lips • Delayed and abnormal dentition

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		• Recessed chin • Small, protruding external ear without earlobes
3.	Cardiovascular	• Myocardial fibrosis, calcification of the mitral valve leaflets and prominent veins often • with easy bruising • Atherosclerosis of the large and small arteries • Severe depletion, attenuation, or change of shape in vascular smooth muscles
4.	Skin	• Thickened, hyalinized skin taut in most places, but loose on fingers and toes • Sebaceous glands may be severely reduced in number • Scleroderma usually beginning on lower abdomen, proximal limbs and buttocks
5.	Hair and nails	• "Plucked bird" appearance with scalp hair progressively diminishing to a few • Remaining blonde or white, fine, fuzzy and brittle hairs. Eyelashes and brows are often lost • Nails usually small, thin and dystrophic, but may also be thick
6.	Sexual	• Sexual maturation is absent • Males are aspermatogenic; females have ovaries with primordial follicles • Nipples may be hypoplastic
7.	Muscles	• Generalized muscle atrophy, protruding abdomen, poor muscle development
8.	Metabolic	• Failure to thrive and progressive loss of subcutaneous fat • Weight and height below the third percentile

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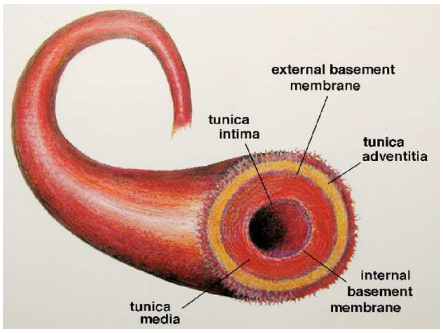

Fig. 1 ***Arterial features***

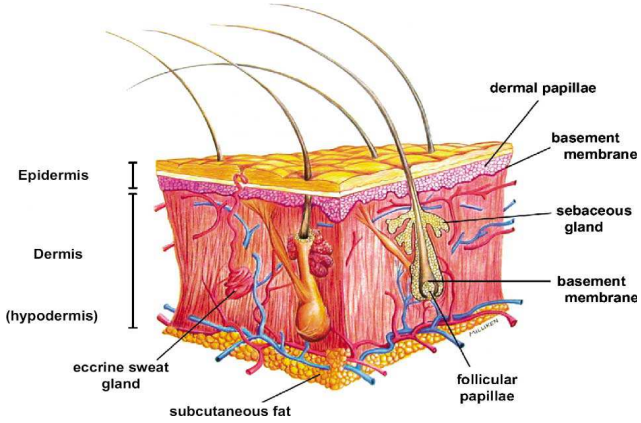

Figure 2:- Structures of skin and hair

➢ *ATHEROSCLEROSIS IN HUTCHINSON–GILFORD PROGERIA*

Most people with HGP die before age 20 from myocardial ischemia secondary to atherosclerosis and associated degenerative mitral and aortic valve disease. High serum cholesterol and triglyceride levels are probably not the cause because while not rare, they are also not always present and in some cases they are low[24]. Normal arteries have three layers (Figure:-1): a tough, outer tunica adventitia; an elastic tunica media, composed mostly of smooth muscle cells; and a thin, inner lining called the tunica intima.

Each of these regions is separated from its neighbour by a basement membrane. Basement membranes are thin sheets of extracellular matrix that provide a barrier (and sometimes, a filter) that separates epithelial cells from underlying connective tissue and that supplies an anchor to which cells and tissues can connect. As noted, there are two basement membranes in arteries. The external basement membrane separates the adventitia from the media and the internal basement membrane provides a similar separation between the media and intima. As in most basement membranes those of the arteries contain cross branded fibrils of types I and III collagen which lend strength and elasticity respectively. The diameter of these collagen fibrils varies across the width of the artery, the thickest fibrils being found in the adventitia (50–100 nm) where more strength is required, and the thinnest fibrils being found in the intima (30–40 nm) with intermediate diameters in the media [25].

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In HGP changes in arteries have much in common with changes in familial atherosclerosis[26, 27]. Specifically, detailed autopsies of HGP arteries have found dystrophic basement membranes depleted of smooth muscle cells, which appeared to have been disintegrated by hemodynamic stress. All basement membrane collagens were present in normal distribution with one exception; type I collagen was missing from the adventitia and media and from both the external and internal basement membranes. Type I collagen was, however, over represented in the intima where the fibrils were half normal size with frayed edges and sometimes irregularly dispersed. This size observation is interesting because it is not seen in either familial atherosclerosis. Type III collagen, which normally combines with type I in arteries, was not over represented in the intima, but rather, was found, as usual, in all three arterial layers. Overall, these results give the impression that type I collagen has migrated from the outer layers of the artery to the intima. Migration of type I collagen might also explain the disintegration of smooth muscles in HGP; collagen fragments have been shown to cause smooth muscle cells to lose adhesion and to round up in vitro[28] and this result has been used to link collagen to smooth muscle cell degradation in atherosclerosis.

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➢ *SKIN AND SCLERODERMA IN HGPS*

Normal skin has three components of interest to this discussion: epidermis; basement membrane; and dermis (Figure:-2). The epidermis contains columns of keratinous cells which arise out of the dermal papillae located just above the basement membrane. Below the basement membrane lies the dermis, often described as a dense feltwork of collagen and elastic tissue intermixed with a few cells. The dermis supports the cutaneous appendages, such as hair follicles, sebaceous and sweat glands. The lowest part of the dermis contains subcutaneous fat cells. In Hutchinson–Gilford progeria, scleroderma usually appears at age 6–12 months, typically at the hips and proximal extremities. The skin becomes thick at first, but may in later stages become thin and shiny. Histologically the upper epidermis seems healthy but at its base it begins to lose integrity. On the underside of the basement membrane, in the dermis, the changes are more dramatic. Normally the upper part of the dermis contains relatively thin collagen, with the diameter of fibrils increasing with depth[29]. Now, however, the situation is reversed. The upper dermis contains thick bundles of collagen, while in the lower dermis, the bundles are exceptionally thin (10–40 nm versus the normal 70 nm) and homogenized. Deeper down, in the subcutaneous tissue, the connective septa contain thin, wavy, collagen bundles and large amounts of proteoglycans involved in collagen assembly. Over time the outer skin develops a progressive, mottled hyperpigmentation without photosensitivity, while in the dermis, subcutaneous fat often disappears entirely.

Skin appendages are also affected in HGPS. Children with HGPS have normal, often thick hair at birth, but in the first 12 months it begins to thin. The rate of loss varies, but the progression is always towards a “plucked bird” appearance characterized by fine, sparse, fuzzy and sometimes brittle and broken hair. The basement membrane of hair is contiguous with the dermal basement membrane and, other than in minor ways, the follicular papillae that regulate hair diameter are different from dermal papillae in name, but not in physiology. The sebaceous glands, which are often reduced in frequency in HGPS, are also lined with dermal basement membrane.

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THE LAMINS

The lamins are type-V intermediate filament (IF) proteins located in the nucleus, primarily in the nuclear periphery, underlying the nuclear envelope. The lamins consist of the A and B types. Both types share the structural features of having a small globular domain at the amino terminus and a larger globular domain at the C terminus, separated by a rod domain of a-helical coiled coils[30]. A largely undeciphered process of dimerization, multimerization and higher-order assembly produces a network of lamin IFs, which comprise the 20–50 nm thick nuclear lamina. The nuclear lamina structurally supports the nuclear envelope (NE) and largely determines the overall shape of the interphase nucleus[31]. In addition, the lamina associates with chromatin both directly and indirectly and has been implicated in the regulation of gene expression and in DNA synthesis[32]. Two separate genes, lamin B gene 1 (LMNB1) and lamin B gene 2 (LMNB2), encode the B type lamins[33], whereas A-type lamins arise by alternative splicing of the single lamin A gene (LMNA gene) on human chromosome 1[34]. In LMNA the first 566 amino acids are common to both lamins A and C.

Lamin A has an additional 98 amino acids at the carboxy terminus, whereas Lamin C has only six unique carboxy amino acids. Both lamins A and C appear to be incorporated into the nuclear lamina at relatively equivalent ratios. A-type and B-type lamins differ in their expression patterns during development and in certain adult cell types[35, 36], as well as in their behavior during disassembly and reassembly of the NE during cell division[37]. A series of post-translational modifications facilitate the assembly of lamin A and B-type lamins into the lamina. Lamin A and the B-type lamins are farnesylated at a CaaX motif (where C is cysteine, A is any amino acid with an aliphatic side chain and X is any amino acid) in the carboxyl terminus. This lipid moiety results in the insertion of the lamins into the inner nuclear membrane. Subsequent cleavage produces a mature membrane bound form of the lamin proteins. Lamin C, which lacks a farnesylation site, relies on the prior incorporation of Lamin A for its inclusion into the nuclear lamina[38, 39]. Figure 1 shows a representative presentation of lamins in the nucleus

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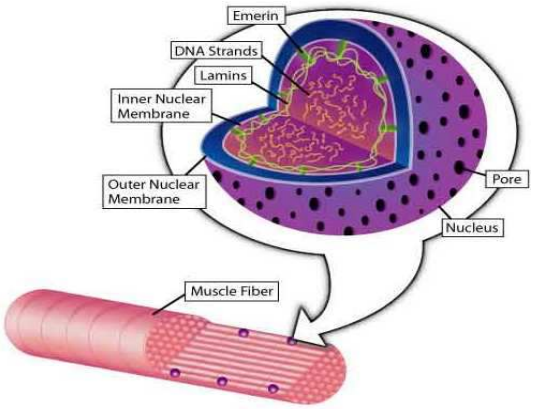

Figure 3:- Lamins in nucleus

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DISEASE MECHANISMS

Because the A-type lamins are expressed in the majority of adult cells and tissues, mutations in Lamin A (LMNA) and cells from patients with one of several laminopathies, including the Progeria, reveal dramatic defects in nuclear envelope structure. The nuclei show frequent blebbing or 'herniations', including large-scale alterations in nuclear shape, increased separation of the inner and outer nuclear membranes, clustering of nuclear pores, loss of some inner nuclear membrane (INM) proteins from one pole of the nucleus and disruption of the underlying electron-dense heterochromatin[31, 40, 41]. On the basis of these observations, the suggestion arose that nuclei containing defective lamins may be mechanically more fragile than their wild-type counterparts and that this fragility may ultimately lead to nuclear damage and cell death. Direct analysis of the mechanical properties of the Lmna fibroblast nuclei in response to physical stretching of the cells revealed that the nuclei were indeed less rigid than normal wild-type nuclei[42].

The LMNA fibroblasts also showed diminished activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway and were more prone to apoptosis and necrosis than normal fibroblasts when subjected to repetitive mechanical stress[42]. This evidence for enhanced nuclear fragility is particularly attractive as an explanation for the cardiac and skeletal muscle pathologies as the forces generated during muscle contraction could potentially lead to preferential breakage of nuclei containing a defective nuclear lamina. Nuclei in non-contractile tissues might remain relatively unaffected despite displaying abnormal nuclear organization. Similarly, effects on the mechanical integrity of nuclei may help explain the susceptibility of HGPS patients to arthrosclerosis and cardiovascular disease[43], as much evidence has indicated that mechanical weakening of the vascular endothelial and smooth muscle cells may be the initial pathological event leading to arthrosclerosis[44].

However, it may still be the case that in for example Progeria the number of affected cells is significantly increased, resulting in a laminopathy. Disruption of the lamina and its associated proteins may affect other cellular processes, such as signaling pathways, including the NF-kB pathway as described above[42]. In addition, the mutations could disrupt interactions between the lamins and chromatin or other nuclear proteins. Indeed it has been suggested that mutations in the carboxy globular domain that cause familial partial lipodystrophy (FPLD) and mandibuloacral disease (MAD) are due to perturbations in the interactions between Lamin A and other proteins, such as the cholesterol synthesis regulator SREBP1[45, 46, 47]. The effects Progerin has on the nuclear envelope (NE) and how this aberrant form of Lamin A can wreak so much havoc in individuals remains to be determined. Structural predictions suggest that the 50-amino-acid deletion may affect post-translational modifications required for A-type lamin integration into the inner nuclear membrane (INM) and lamina. By contrast, Lamin C would be unaffected as its termination codon occurs before the truncation, although any effect on A-type lamin integration into the INM may compromise Lamin C integration[39]. Preliminary data suggest that Progerin is able to integrate into the lamina, although Progerin is present at a low level compared to the levels of intact full length lamin A still produced[12]. Fibroblast cultures from HGPS patients appear to have a reduced rate of proliferation, altered expression levels of genes regulating the cell cycle

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and a slight increase in aneuploidy[48, 49]. This raises the possibility that growth retardation and delayed maturation in some of the tissues in HGPS may arise as a result of a postnatal defect in cell proliferation. These observations also suggest the existence of a developmentally mediated mechanism directing how cells proliferate in response to a defect in the lamins.

CONCLUSION

Progeria in humans is caused by mutations in either of the genes for Lamin A/B or in the Werner's RecQ DNA helicase. Much indirect evidence has suggested that other experimentally induced premature ageing phenotypes are induced by inhibiting the DNA repair process. The identification of Progerin and other mutant forms of the Lamins as a cause of progeria has only recently been established. There is already much evidence indicating that the lamins have multiple functions within the nucleus in organizing chromatin, maintaining nuclear shape and regulating DNA synthesis. It however remains to be determined what role the lamins have in maintaining genome integrity and possibly DNA repair mechanisms, which, when perturbed, may result in progeria and ageing. Analyzing the consequences of the lamin mutations in cells has provided some clues as to how progeria develops. Together, these findings suggest that proper expression and function of the lamins play a key role in maintaining cell and tissue integrity during ageing. Thus, finding HGPS to be the result of pathogenesis rather than the result of true ageing may be exactly what we require for increasing understanding of the ageing process.

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