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HUTCHINSON-GILFORD SYNDROME

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ABSTRACT. It is a rare genetic disease, which manifests by an accelerated senescence process of tissues and organs, without mental impairment. We propose an update of the international literature data on the early diagnosis, the therapy (genetic engineering and farnesyltransferase inhibitors) and the prevention of the disease, as well as on the mechanisms involved in its production. We aim to extend the study to cell cultures acquired from Progeria Research Foundation.

Keywords: senescence, lamin, farnesyltransferase inhibitors

GENERAL CONSIDERATIONS

Discovered in 1886 by Jonathan Hutchinson (1) and Hastings Gilford and subsequently termed HGPS (Hutchinson Gilford Progeria Syndrome), this rare genetic disease is mainly characterized by the occurrence of accelerated aging and cardiovascular diseases in children. The term progeria is derived from Greek and it means "premature aging".

Being a latent disease, children affected by progeria die around the age of 12 years, following myocardial infarction or cerebrovascular accident (2, 3, 4). The development of symptoms is comparable to an aging rate 6 to 8 times higher than normal, although certain features characteristics of the age do not occur.

The incidence of the disease is of approximately 1/8 million newborns (5), with a higher frequency reported in Japan. Another form of progeria, i. e. Werner syndrome or adult progeria, has been described in the literature, which, having a much higher incidence, 1/100,000, only appears during puberty, death occurring after the age of 30 years, due to the same symptoms.

HGPS represents a real challenge to researchers, as it can reveal important indications related to the aging process (6).

CAUSES AND BIOCHEMICAL MECHANISMS

HGPS is an autosomal dominant disease, predominantly caused by a de novo mutation, i.e. the substitution of a base in nucleotide 1824 (1824 C $\rightarrow$ T) of codon 608 of exon 11, of the LMNA gene on chromosome 1 (7, 8). The concerned gene is not genetically transmitted, and most frequently, the parent contributes a normal chromosome, which becomes mutant during cell division, the mutation being subsequently replicated.

This gene is responsible for the synthesis of lamin A, a fibrous protein which, along with lamins B and C forms a fibrillar protein network that lines the internal face of the nuclear layer. The three proteins form the nuclear lamin, which determines the shape and the stability of the nucleus (9, 10); at the same time, nuclear lamin interacts with the chromosomes and contributes to the disassembly of the nuclear layer at the beginning of mitosis and to its reassembly at the end of mitosis.

Researchers currently consider that defective lamin A destabilizes the nucleus, a process which is extremely important in this disorder.

LMNA gene mutation leads to the deletion of a fragment of 50 amino acids in prelamin A, resulting in a mutant protein, progerin, which cannot be processed to mature lamin A (11), which causes the damage of cells and their accelerated death.

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Lamin A is synthesized as preprotein (prelamin A) at the level of ribosomes; this is postranslationally processed during several stages. Prelamin A has 3 characteristic sites: at the C-terminal end a CAAX-box (where C is cysteine, A an aliphatic acid, and X any other amino acid), in its proximity a sequence of 14 amino acids that will represent the site of action of a specific enzyme (ZMPSTE24), and at the N-terminal end an area that allows the assembly of the 3 lamins in order to form the network of fibrillar proteins that compose nuclear lamin.

The roles of these sites are multiple. In the first place, the farnesyl group is attached to cysteine within the CAAX-box; the action of the farnesyltransferase enzyme results in the binding of the nascent protein (prelamin A) to the endoplasmic reticulum membrane (12, 13). The farnesyl radical mediates the synthesis of cholesterol, a highly hydrophobic protein that facilitates the insertion of prelamin A into the endoplasmic reticulum membrane. During the following stage, the terminal three amino acids from the CAAX-box are cleaved by the ZMPSTE 24 enzyme, and terminal cysteine is carboxymethylated with the participation of a methyltransferase; subsequently, the ZMPSTE 24 enzyme causes the cleavage of 14 amino acids towards the N-terminal end, including farnesylated cysteine, releasing the protein from the endoplasmic reticulum into the cytosol, which can thus be transported and internalized into the nucleus (14, 15).

It seems that the fixation of prelamin A to the endoplasmic reticulum membrane allows its postranslational processing and the obtaining of mature lamin A capable of penetrating into the nucleus. In the case of mutant prelamin A, the 1824 C $\rightarrow$ T mutation does not cause the substitution of an amino acid in progerin, compared to functional prelamin A.

It rather generates an aberrant splicing of messenger RNA, resulting in the deletion of 50 amino acids from the C-terminal end and the formation of progerin. The consequence of this deletion is the loss of the target area (the 14 amino acids) for the enzyme ZMPSTE 24. Consequently, progerin remains farnesylated and bound to the endoplasmic reticulum membrane without the possibility of being released into the cytosol. However, the protein finds the way to the nucleus by diffusion through the endoplasmic reticulum, which is situated in the proximity of the outer nuclear membrane, but its binding to the farnesyl radical makes impossible the construction of nuclear lamin.

The result is the distortion of the nuclear membrane and an abnormal binding of chromatin to the nuclear layer. The distorted nuclear membrane is susceptible to mechanical damage, causing an increase in cell death and implicitly, the appearance of symptoms of premature aging in progeria. The destruction of chromatin or its binding to the defective nuclear lamin leads to deregulations in the gene expression and implicitly in the cell cycle, nuclear lamin playing a role in DNA replication and repair. In this case, these processes are deficient; in fact, unrepaired DNA lesions are evidenced in a higher proportion in the fibroblasts of patients with progeria.

Since farnesylation mediates the penetration of progerin into the nucleus and the attachment of progerin to the inner membrane of the nucleus, it might be inferred that the disease is prevented through the inhibition of farnesylation.

ALTERNATIVE THEORIES

One of the generally accepted theories of cell aging results from the incapacity to read, repair or replicate the DNA, as the aging process can also be correlated with the shortening of telomeres. Telomeres, repeat DNA sequences at the end of chromosomes, represent “the molecular clock of cell aging”. Their shortening during life is a normal process, taking place each time when the cell is divided. After several divisions, chromosomes reach a critical length and can no longer replicate; thus, the aged cell dies (16). In cells affected by progeria, telomeres are short and prevent DNA replication when their length is critical; this allows the potential DNA lesions not to be submitted to the action

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of the repairing system, which results in the appearance of various symptoms associated with progeria (17). A treatment with telomerase, which is an enzyme that maintains the length of telomeres, was experimentally tested; however, their use increases the risk of transformation of healthy cells into cancer cells.

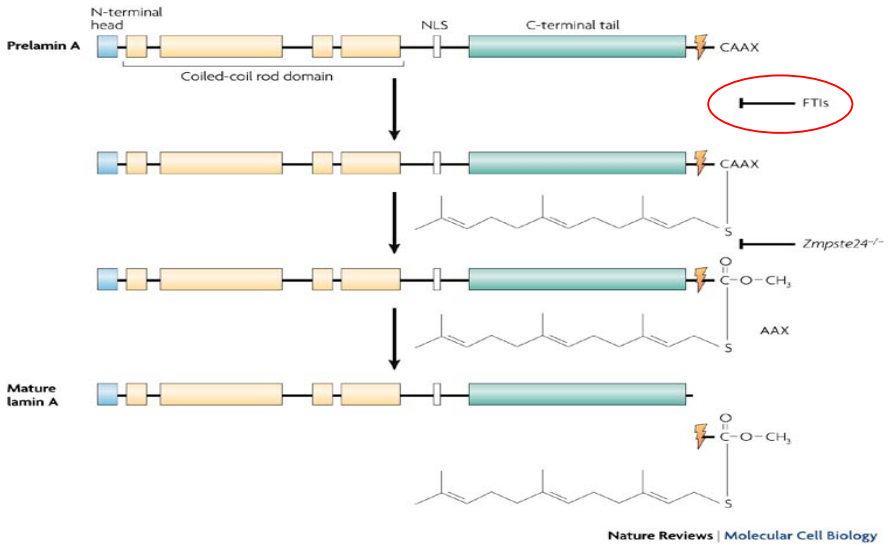

Fig. 1 Synthesis of lamin A

The appearance of progeroid syndromes can also be correlated with a mutation in the DNA-helicase enzyme, involved in semi-conservative DNA replication. Not least, cell aging is a biological process determined by the rate at which free radicals are assimilated in the organism, destroying cells, attacking tissues and affecting vital functions, which is why they can be correlated with the appearance of progeria.

CLINICAL MANIFESTATIONS

During the first 14-24 months of extrauterine life, children seem healthy, although some features such as facial cyanosis (a blue-violet color of the face, due to insufficient blood oxygenation), a sharp nose, may indicate the presence of the disease at birth.

Clinical manifestations include almost invariably a small stature, an obviously smaller weight than normal in relation to length, low subcutaneous fat, generalized alopecia, bone deformation (pyriform chest, clavicular and mandibular hypoplasia, craniofacial disproportion, an abnormal position of the body, coxa valga, osteoporosis), stiff joints, failure of complete sexual development. Other common characteristics are thin, dry, wrinkled skin, with brown spots in different regions, prominent superficial veins, particularly those of the scalp, loss of eyelashes and eyebrows, thin lips, prominent ears, absence of ear lobes, shrill voice and dystrophic nails. Fig. 2

Patients usually show severe atherosclerosis and death occurs as a result of complications caused by diseases of the cardiac and cerebrovascular systems (arthritis, CVA, heart failure). Surprisingly, in spite of multiple deregulations, subjects present a normal mental development, without mental retardation, and sometimes have an intelligence quotient above the mean (18, 19).

THERAPEUTIC METHODS

In the course of time, various therapies have been attempted, but none has been proved to cure progeria. However, there are theories based on clinical research that can develop into future treatments. Patients with progeria usually have a low amount of antioxidants in the organism; so that in order to fight oxidative stress, immediate solutions

are applied: therapy with vitamin E, coenzyme Q10, lipoic acid. In addition to its encouraging growth effects, STH has strong anabolic properties. The administration of this hormone improves some catabolic effects of normal aging, but has no effect on the progression 9000100114042 of atherosclerosis in patients with progeria.

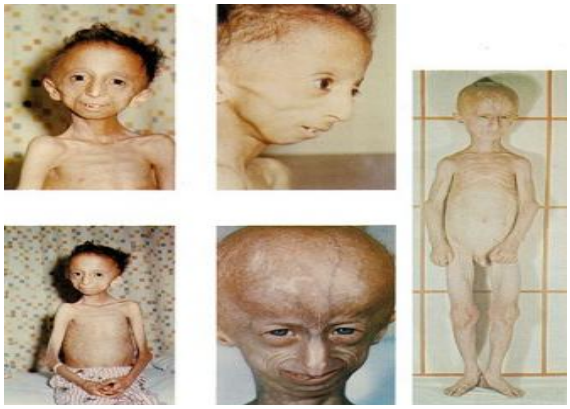

Fig. 2 Clinical aspect (19)

Because farnesyl is an intermediate agent of cholesterol synthesis, the administration of anti-hypercholesterolemic drugs (statins) might diminish the evolution of progeroid syndromes. Hydrotherapy for the improvement of pain and the prevention of the progression of arthritis is also recommended. Aspirin, due to its anticoagulant effect, is administered in order to reduce the risk of infarction. The treatment of these patients should also be correlated with psychological assistance (5).

THERAPEUTIC PERSPECTIVES

Clinical research currently follows three directions. In the first place, genetic engineering aims at the synthesis of genes that encode for functional lamin A and their implantation in affected subjects. In the second place, the manipulation of the length of telomeres by means of telomerase can also be a potential therapy of this disease.

The most recent studies published in the literature indicate as a possible therapy in progeria the so-called farnesyltransferase inhibitors (FTI), such as Lonafarnib and Tipifarnib (20). FTIs represent a class of drugs currently tested in disorders such as myeloid leukemia and neurofibromatosis. Due to their low toxicity, they were initially used for the inhibition of certain cancer-causing proteins which require farnesylation in order to function (21).

In progeria, FTIs act by inhibiting the attachment of the farnesyl group to prelamin A. Fig. 1. Because farnesylation does not take place, mutant prelamin A does not bind to the endoplasmic reticulum membrane, but is degraded into component amino acids that enter the cell reservoir, the role of lamin A being taken over by lamins B and C. Thus, the harmful properties of progerin, whose synthesis is suppressed, are diminished. At the same time, these inhibitors have the capacity to reduce the abnormal structure of the progeroid cell nucleus to one close to normal (22, 23, 24) (Fig 3).

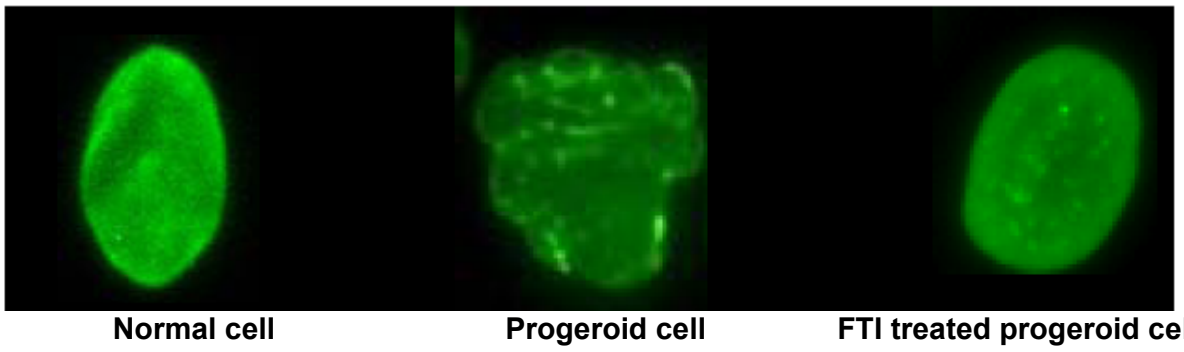

Fig. 3 Action of FTI on the progeroid cell (13)

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CONCLUSIONS

Progeria is a rare genetic disease caused by the defective synthesis of lamin A due to the deletion of the site of action of an enzyme involved in this process.

The main consequence of the disease is premature aging, which occurs by 2 mechanisms: prevention of cell division and destruction of the nucleus followed by cell death at a rate 6-8 times higher than normal.

Therapeutic perspectives follow three directions: prevention of farnesylation, enhancement of telomerase activity and diminution of the action of free radicals.

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