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MINI-REVIEW

Molecular elucidations of hutchinson-gilford progeria syndrome: A hope for managing horrors of premature aging in children

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Abstract: Hutchinson-Gilford progeria syndrome (or Progeria) is an exceptionally rare genetic disorder in children. It is caused by a rare point mutation in the lamin gene. It encodes lamin A protein, resulting in the de-shaping of nuclear membrane. This altered structure of the nuclear membrane renders the nucleus unstable. The shortened lifespan of the nucleus makes the cell liable for rapid ageing. Children are healthy by appearance when they are born but the signs appear after 12-24 months of age. Cardiovascular system is greatly affected which became a reason for the death of most of the patients of progeria. Stiffened joints disturb the bone movements; and alopecia affects the appearance of the patient. Rate of occurrence of the disease is one per four hundred thousand of people, though both sexes are equally affected.

Keywords: HGPS, Progeria, Premature aging, nuclear membrane, genetic disorder.

INTRODUCTION

Progressive changes in the cell structure and functions leads to the aging and sometimes cell is liable to rapid and untimely aging due to a number of accumulated defects in the function that leads to the cell death and then failure of the system (Meta, 2006). These defects are related to DNA, such intricate damages could be due to the cell exposure to ionizing radiations, UV light, genotoxins and endogenous mutagens as reactive oxygen intermediated (Rusinol, 2006). All these factors result in impaired enzyme functions so the cell metabolism and maintenance processes are weakened, and enzymatic system is not capable to maintain replicate fidelity of the genome of the cell. Irrespective of these external factors, persons with gene mutation clearly depicts the quick aging phenotypes and have limited life span (Scaffidi *et al*, 2005). Hutchinson-Gilford progeria syndrome (or progeria) is a unique autosomal-dominant disorder which is being characterized by the premature or early appearance of signs of aging.

It refers great insight to the science of accelerated premature aging. Gradual advance in the knowledge of getting old has provided us the basis of progeria. Certain features of normal ageing like neurocognitive disorders and increase cancer liability are relatively less prominent in progeria (Hennekam, 2006).

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Clinical findings

The nuclear lamina is a network of structural filaments composed of A and B type lamins, positioned at the nuclear envelope and all through the nucleus. The Lamin filaments make available mechanical stability and support to the nucleus for many crucial activities, counting gene regulation (Farnsworth *et al*., 1989). The disease is characterized mainly by, "wrinkled old man" facial appearance. The children affected may have huge skull and there is Bird-like facial appearance. There is atrophy in the muscles and skin. Subcutaneous fat is depleted which results in thin wrinkled skin (McClintock *et al*., 2005). Increased concentration of serum lipid levels and predominant sclerosis in the vessels are observed. Teeth are highly impacted earlier or later (Maciel *et al*., 1988). There is a loss of hair of scalp and eyebrows (alopecia), forehead veins become prominent, circumonal cyanosis, convex nasal profile. Intelligence is usually normal. Frequent osteolysis along with less joint mobility is also seen (Hennekam, 2006). The child is normal at birth. Death occurs between the age group of 7-16. Probability of occurrence of the disease in children of both genders is almost same. Death usually caused by the outcomes of arteriosclerosis, increased chances of myocardial infarctions or transient ischemic attacks. Still it is not worthy that despite of cardiovascular system and growth most of other vital organs like brain, lungs, kidney and gastrointestinal track remain unaffected. Advanced technology has lead in access of the diagnosis of the disorder (Qadir and Faheem, 2017; Qadir *et al,* 2018a).

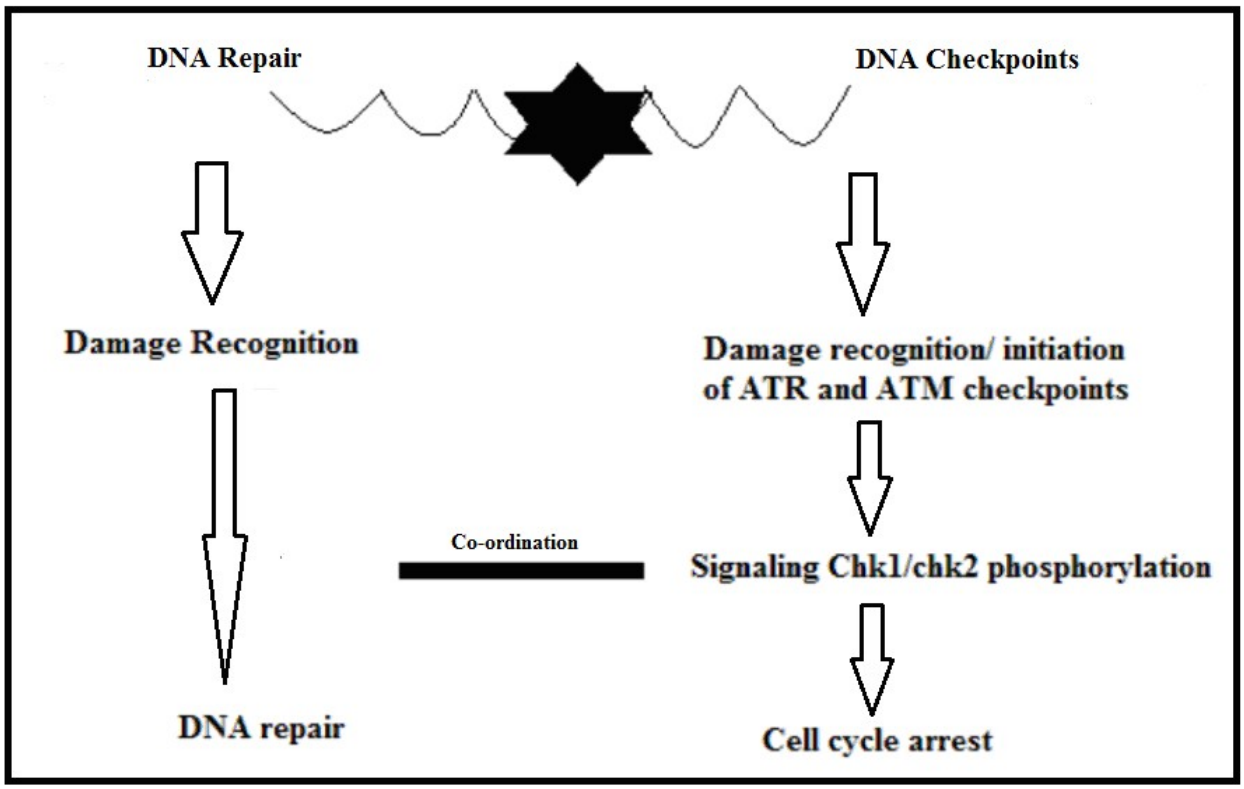

Fig. 1: DNA damage responses in human cell, two major cellular pathways i.e. damage recognition check points and DNA repair are activated to restore and conceal the DNA damage. DNA checkpoints are noticed to be persistently activated by the DNA damage in progeroid cells. But continuous activation of the checkpoints result in relatively delayed DNA repair. It is one of the major causes of genomic instability in Hutchinson-Gilford progeria syndrome.

Cellular defects associated with progeria are related to the buildup of mutant protein progein inside the nuclear membrane of the vascular endothelial and smooth muscle cells (McClintock *et al*., 2006). The increased concentration of this mutant protein in the nuclear membrane is responsible for decrease in cell life span.

An introduction to lmna gene structure and function

The LMNA gene encodes for the LMNA proteins which also sometime called as lamins. LMNA is official symbol related to both lamin A and C genes. The two chief proteins produced are, lamin A and C together known as intermediate filament protein. These proteins have approximately identical sequence of protein building blocks (amino acids). As far as the size is concerned lamin A is a little nuclear envelope (the membranous boundary of nucleus). The inner membrane of the nucleus is attached to the mesh frame work of intermediate filaments which is constituted by the both lamin proteins (Lammerding *et al*., 2005). This nuclear membrane not only involved in regulation of in and out movement of certain molecules through the nucleus rather it is also involved in gene expression and regulation. Lamin A is processed inside nucleus before becoming a part of the nuclear lamina. Any mutation leading to inefficient binding, structural differentiation and splicing of both genes result in many genetic disorders one of which is Hutchinson-Gilford progeria syndrome (or progeria) mainly occurred due to a point mutation in lamin A and it is not related to lamin C.

Mutation in lamin: The cause of progeria

Initially progeria was contemplated to be an autosomal disease with recessive criteria (Khalifa, 1989; Maciel, 1988). Current facts have suggested that the progeria is caused by point mutation in Lamin gene (De Sandre-Giovannoli, 2003). The mutated gene locus is recognized to be located on a small region of chromosome 1q (Eriksson, 2003).

The lamin gene is constructed of 12 exons. In the course of unconventional splicing, it gives rise to two major proteins, lamin A a large gene and lamin C a relatively shorter one. This alternative splicing site is located on exon 10. But mutation for progeria is in exon 11 thus it has no effects on lamin C. Sequencing of *LMNA*, in this case and in other previously concerned cases of heritable disorder (Young, 2006) revealed that typical cases of HGPS has a pronounced point mutation G608 (that is never inherited) single base changeover, (GGC > GGT), within exon 11.

Posttranslational processing

In order to manufacture a mature lamin A protein many Posttranslational processing occur within the cell. These posttranslational processes need a cascade, "CaaX" (conserved COOH-terminal, sometimes, also called as CaaX motif of nuclear lamins, may play a role in targeting newly synthesized proteins to the nuclear envelope) containing prelamin A (664 amino acids). This "CaaX" motif is present at the 3' end of prelamin A. This 4–amino acid tail (CAAX motif C is a cysteine ,"aa" means aliphatic amino acids and the X stands for any one of several amino acids) is a detection site for modification of posttranslational processing (Scaffidi *et al*., 2005). To this "Caax" motif a 15-carbon group which is farnesylated is added. The functional criterion of farnesylation is to enable the lamin proteins to get attached to the nuclear membrane lamina. After farnesylation the "aaX" portion of "caaX" motif is being replaced by a carboxymethyl group. This process is being carried out by an enzyme called ZMPSTE24 (Scaffidi, 2006).

Single nucleotide substitution

Patients with classical progeria have a point mutation in DNA building blocks, this mutation is caused by single nucleotide substitution in exon 11 of the prelamin gene, GGC→GGT, replacement of cytosine with thymine occurs at 1824 position. This transmutation is not associated with structural alternation of the lamin proteins rather it induce alternative splicing sites. It happens due to removal of a part of exon 11, removed part is comprised of 150 amino acids having the recognition site for ZEMPSTE24 enzyme. As the mutation does not interfere with exon 12 the first three steps of posttranslational process i.e, farnesylation of CaaX site and subsequent removal of the aaX, and addition of the carboxy methyl group, remains unaffected but the cleavage of C-terminal component of the molecule fails to take place (Goldman *et al*., 2003)

Progerin or mutant prelamin A

This new molecule produced as a result of mutation of the exon 11 proteins, is called "progerin" this mutant progerin or prelamin A due to the deletion of 150 amino acids remains farnesylated thus it hang about entrenched in the nuclear membrane lamina. Due to the accumulation of great concentration of progerin in the nuclear membrane rather than the mature lamin A protein "deshaping" or "nuclear blebbing" results (Young, 2005). The progerin is largely accumulated in the cadiac and smooth muscle cell nuclear membrane (Houben *et al*., 2007). It adversely affects the life span of an intact cell resulting in cardiovasculopathy and other adversaries of the cardiovascular and connective tissues.

TREATMENT

Previously, Hutchinson-Gilford progeria syndrome has been managed by treating the symptoms, but with the knowledge of molecular biology of the disease, we have different options to manage Hutchinson-Gilford progeria syndrome (Strandgren *et al*., 2017). Targeting prelamin A processing, Blocking progerin and lamin A splicing, Modifying progerin interactions and turnover in the nucleus, Targeting proteins in the nucleus affected by progerin, Targeting cytoplasmic functions affected by progerin, and Cellular reprogramming and tissue regeneration are the main options to manage the disease. Advanced technology has lead in the better management of the disorder (Janbaz *et al,* 2012; Javed *et al,* 2011; Qadir, 2009; Qadir, 2010; Qadir, 2011; Qadir, 2016; Qadir, 2017a; Qadir, 2017b; Qadir*,* 2018a; Qadir*,* 2018b; Qadir *et al,* 2018b; Qadir and Anwer, 2019).

CONCLUSION

The mutation in the lamin A gene causes the abnormal production of lamin A protein. Proteins of Lamin family has significant role in maintaining the cellular structure. Lamin A protein being an important part of nuclear lamina deterioration of the nuclear envelop though it is a timely process but accumulation of the abnormal progerin or Lamin A protein cause nuclear blebbing, therefore interfere with normal life span of a cell. Life time of cells with mutation is decreased to a great extent. Cardiac cells and smooth muscle cells occur as predilection site of the progeria. It is still enigma that why there is selectivity in the sites for adversaries. The effected child is normal at the time of birth but with passage of time signs of progeria starts revealing the underlying anomaly. The physical appearance of the patient suffers badly. Patient's health rapidly falls apart and there is no turning back of clock.

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