PROGERIA SYNDROME: A PREMATURE AGING DISEASE

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Aging is an inevitable consequence of human life resulting in a gradual deterioration of cell, tissue and organismal function and an increased risk to develop chronic ailments. Premature aging syndromes, also known as progeroid syndromes, recapitulate many clinical features of normal aging and offer a unique opportunity to elucidate fundamental mechanisms that contribute to human aging. Progeroid syndromes can be broadly classified into those caused by perturbations of the nuclear lamina, a meshwork of proteins located underneath the inner nuclear membrane (laminopathies); and a second group that is caused by mutations that directly impair DNA replication and repair. Hutchinson-Gilford Progeria (HGPS) is an accelerated aging syndrome caused by a mutation in lamin A and one of the best studied laminopathies. HGPS patients exhibit clinical characteristics of premature aging, including alopecia, aberrant pigmentation, loss of subcutaneous fat and die in their teens as a result of atherosclerosis and cardiovascular complications. Lamin A is an inner nuclear membrane protein with both structural and cell signaling effects. The single C to T transition at nucleotide 1824 of LMNA does not change the translated amino acid (Gly608Gly), but activates a cryptic splice site, resulting in the deletion of 150 base pairs in the 3' portion of exon 11. Translation followed by post-translational processing of this altered mRNA produces a shortened abnormal prelamin A protein with a 50 amino-acid deletion, henceforth called "progerin". A key to disease in HGPS is the presumably persistent farnesylation of progerin, which renders it permanently intercalated into the inner nuclear membrane where it can accumulate and exert progressively more damage to cells as they age. The inability to release progerin from the nuclear membrane results in structural stress on the nucleus. It is hypothesized that this permanently farnesylated mutant form of prelamin A (progerin) leads to the progressive defects in nuclear architecture that are seen in HGPS. Although rare, HGPS remains a great concern for its array of debilitating effects. Even more frustrating perhaps is its resistance to therapies. Despite knowing its exact location, 1q21.2, its somatic virulence eludes direct combat, relegating most medical interventions to high-calorie diets, careful playing with other children, and persistence. Progress in research on HGPS has led to a rapidly increasing number of therapeutic candidates; however, similar to the case of physiological aging, currently there is no cure for HPGS.

In summary, HGPS is a progeroid syndrome which has attracted extensive research interest partly because it might provide a window into the mechanism and treatment of physiological aging. Although copious barriers have to be overcome before a cure for HGPS can be developed, with increasing understanding of the molecular mechanism of the disease, more therapeutic targets are expected to be identified. Along with the continuous enhancement in the design of treatment strategies, the emergence of a cure is only a matter of time.