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Uncovering the trail behind growing too old, too soon

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Scientists from A*STAR's Institute of Medical Biology (IMB) in Singapore and the University of Hong Kong's Department of Medicine have produced the world's first human cell model of progeria, a disease resulting in severe premature ageing in one in four to eight million children worldwide. This model has allowed them to make new discoveries concerning the mechanism by which progeria works. Their findings were published this month in the prestigious scientific journal, *Cell Stem Cell*(1).

Hutchinson-Gilford Progeria Syndrome, also known as progeria, is caused by a mutation in the gene encoding for the protein lamin A, an important component of the membrane surrounding a cell's nucleus. The mutation results in a truncated form of lamin A called progerin, which in turn causes misshapen cell nuclei and DNA damage. Children with progeria suffer symptoms of premature ageing, including growth retardation, baldness, and atherosclerosis (hardened arteries), and all die in their early teens from either heart attack or stroke.

Led by IMB's Profs Alan Colman and Colin Stewart, the team used a novel technique of deriving induced pluripotent stem (iPS) cells from cells of human progeria patients. This human progeria model allows the group to trace and analyse the distinctive characteristics of progeria as it progresses in human cells. Previously, only mouse models of the disease were available.

Said Prof Colman, "While mouse models of progeria have been

informative, no one mouse model recapitulates all the symptoms seen in humans. Our human progeria model allows us to examine the pathology of the disease at a much closer resolution than previously possible."

The researchers used their iPS cells to identify two types of cells - mesenchymal stem cells (MSCs) and vascular smooth muscle cells (VSMCs) – that were particularly adversely affected by progeria. This means that a young patient with progeria would typically have fewer MSCs and VSMCs than other children. MSCs were found to be very sensitive to a low oxygen environment and their losses could delay renewal of the various tissues they gave rise to, thus exacerbating the patient's symptoms of ageing. The same effect on VSMCs could explain why their number was reduced in the patient's heart vessels.

Background

The group's findings are a significant boost to existing research on over 10 diseases associated with lamin gene mutations. Prof Stewart previously led a study in mice at IMB showing that progeria affected the connective tissues, potentially via defects in a signaling pathway connecting the nuclear lamina with the extracellular matrix (2) and which was associated with death of the smooth muscle in major blood vessels.

Said Prof Stewart, "This new study provides further evidence for the role of lamin processing in connective tissue function, as well as insights into the normal ageing process. We hope to soon find new routes of intervention to treat this incurable disease. Such interventions may be of use in treating atherosclerosis in general, a condition afflicting many millions of individuals."

More information: References:

(1) A Human iPSC Model of Hutchinson Gilford Progeria Reveals Vascular Smooth Muscle and Mesenchymal Stem Cell Defects. 7 Jan 2011. Cell Stem Cell, Volume x, Issue y. DOI: 10.1016/j.stem.2010.12.002

(2) Functional Coupling between the Extracellular Matrix and Nuclear Lamina by Wnt Signaling in Progeria. Developmental Cell, 2010; 19 (3): 413-425 DOI: 10.1016/j.devcel.2010.08.013

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