Adult stem cell changes underlie rare genetic disease associated with accelerated aging

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Adult stem cells may provide an explanation for the cause of a Hutchinson-Gilford Progeria Syndrome (HGPS), a rare disease that causes premature aging in children, according to researchers at the National Cancer Institute (NCI), part of the National Institutes of Health. These findings, the first to indicate a biological basis for the clinical features of HGPS, also known as progeria, may also provide new insights into the biological mechanisms of normal aging. The results were published in the March, 2008, issue of *Nature Cell Biology*.

“Studies like this of the biology of HGPS hold the potential to benefit children suffering this terrible illness and enlighten us as to the medical changes we all experience as we grow older.” said NCI Director John E. Niederhuber, M.D. “As our population ages, we have an increasing need for greater understanding of the biology of aging and age-related illness, such as cancer.”

HGPS is an extremely rare hereditary genetic disease of children characterized by signs of premature aging. Children with HGPS generally experience the first symptoms by the age of one, and on average succumb around the age of 15, almost exclusively from premature, progressive heart disease. HGPS occurs in one out of four to eight million births; only 100 patients have been documented in the medical literature. Because its striking cardiovascular effects and other clinical features are so closely associated with the normal aging process, HGPS holds great interest for researchers studying age-related biological changes and disease.

The cause of HGPS, a mutated protein called progerin, was identified in 2003. However, the mechanism by which progerin causes the widespread clinical effects of HGPS has been unclear. To forge this link between molecular biology and medical outcome, Tom Misteli, Ph.D., head of the Cell Biology of Genomes Group at NCI's Center for Cancer Research (CCR), and CCR staff scientist Paola Scaffidi, Ph.D., examined the effects of progerin on gene expression in a laboratory model of HGPS. They found that progerin activates genes involved in the Notch signaling pathway, a major regulator of stem cell differentiation -- the process by which stem cells give rise to the mature cells that make up different tissues.

Because most of the tissues affected by HGPS (e.g., skin, fat, muscles, bone, and blood vessels) arise from a common developmental pathway, Misteli and Scaffidi looked at the effects of progerin on adult mesenchymal stem cells, the common cellular ancestor of these tissue types. An adult stem can renew itself, and can differentiate to yield the major specialized cell types of the tissue or organ. Their experiments revealed that progerin profoundly affects the fate of these stem cells, greatly skewing the rate at which they mature into different tissues.

For instance, progerin-producing stem cells showed accelerated maturation into bone but failed to develop into fat. This could explain two of the distinguishing clinical features of HGPS: abnormal bone growth and an almost complete loss of the fatty tissues normally found just beneath the skin. The researchers were able to mimic the progerin's effects in these stem cells by experimentally activating the same components of the Notch pathway targeted by progerin.

Taken together, the results of these experiments provide a new window into the biology behind the clinical features of HGPS. They may also hold relevance for understanding the biology of normal aging. "Progerin is present at low levels in the cells of healthy people," said Misteli. "One

could envision a scenario in which progerin's effects on the Notch pathway and, by extension, on adult stem cells could, over time, lead to many of the tissue changes we commonly associate with the aging process."

Source: National Cancer Institute