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Editorial

Research on Hutchinson-Gilford Progeria Syndrome

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IN this issue of the Journal, I have included a summary of a workshop held in November 2007 on the topic of Hutchinson-Gilford Progeria Syndrome (HGPS) (1). This syndrome was first described over 120 years ago by Hutchinson (2), and although the phenotype does include some aging-like changes, biogerontologists have questioned whether it is a viable model for studying accelerated aging (3). The question has justifiably risen again with the recent identification of LMNA as the gene responsible for this sporadic autosomal dominant syndrome (4).

It is now clear that the syndrome results from the accumulation of a metabolite formed during processing of the mutated pre-lamin A protein. This metabolite has been named progerin, and it induces nuclear blebbing in HGPS cells grown in culture (5), suggesting that serious disruption of DNA metabolism may be occurring in these cells. At least several outcomes are possible, including induction of cell senescence, induction of apoptosis, dysregulated gene expression, dysregulation of differentiation, and so forth. Whatever the critical defect may be, Kudlow and colleagues (6) have argued that progeroid syndromes, including HGPS, ''might have partial mechanistic overlap with normal aging and therefore might provide uniquely informative opportunities to formulate and test hypotheses regarding the biology of aging and age-dependent disease.'' Warner and Sierra (7) also have suggested such possible overlap. Scaffidi and Misteli (8) have recently shown that small amounts of progerin are produced in normal cells by occasional use of the aberrant splice site used in HGPS cells, but it is not known whether these small amounts actually have any impact on longevity. However, progerin does accumulate in the skin with age in a subset of dermal fibroblasts, suggesting that this could be a possible biomarker of cellular aging (1,9).

Kudlow and colleagues (6) suggest three general approaches to identify such putative mechanistic links between normal aging and accelerated aging models, whether human or murine. Because many mouse mutations that induce progeroid phenotypes share disruption of DNA metabolism as a common feature, they suggest that it would be useful to know what roles lamin A plays in the various DNA transactions important to the proper function of a mammalian cell, such as replication, transcription, repair, and recombination. Progerin has in fact been reported to interfere with mitosis (10) as well as induce DNA damage responses (11). Secondly, they suggest that persistent DNA damage signaling, cell death, and cellular changes may contribute to the pathology of HGPS, and that it is important to determine whether and why these changes are selectively targeted to specific cell lineages and tissues. Finally, a third approach is to look for single nucleotide polymorphisms (SNPs) in the gene for lamin A that associate with longevity; Francis Collins reported at the workshop that four such SNPs have been found in older people (1).

Besides the interesting question of whether HGPS is or is not a valid model of accelerated human aging, the most important translational question is the development of a cure—or at the very least an effective treatment. Numerous studies have reported that farnesyltransferase inhibitors reverse the morphological defects observed in HGPS fibroblasts (12). This provides the basis for the clinical trial currently underway under the direction of Mark Kieran at Children's Hospital in Boston. The primary endpoint is weight gain because failure to grow, starting at about age 2 years, represents a consistent and predictable characteristic of the syndrome. Secondary biomarkers such as alopecia, short stature, subcutaneous fat, bone integrity, and a variety of other abnormalities will also be followed.

However, the ideal solution would be a total cure rather than an ongoing treatment. In trying to understand the underlying cause of HGPS, it may be instructive to ask what causes and ''times'' the onset of growth failure and the subsequent low weight and height gain, and why do mesenchymally derived tissues seem to be most vulnerable (13). Sharpless and DePinho (14) have reviewed mounting evidence that accumulation of damage to cellular macromolecules such as DNA could be one cause of cellular attrition with aging. Continued cellular attrition by apoptosis would result in forced regeneration of tissue cells in response to homeostatic demands, possibly resulting ultimately in an inability of stem cell pools to respond to these demands (15).

Such a process could explain an onset of growth failure, at about 2 years of age, such as observed in HGPS. In addition to DNA damage accumulation in HGPS cells, the aberrant morphology of HGPS nuclei might also trigger the cellular attrition reported by Bridger and Kill (16). HGPS stem cells may also be subject to apoptosis, which would compound the attrition problem. Scaffidi and Misteli (17) have recently reported that progerin ''interferes with the

function of human mesenchymal stem cells (hMSCs). . . and changes their molecular identity and differentiation potential,'' further compounding the cellular attrition problem. Thus, theoretically at least, the ability to repopulate stem cell pools in HGPS patients with normal stem cells injected into circulation holds out some promise of an ultimate cure, assuming such normal cells would find the niches and successfully compete with HGPS stem cells to repopulate the niches with healthy cells.

These interesting questions and possibilities justify a continuing interest in basic research on both human and murine progeroid syndromes, and the Progeria Research Foundation will continue to play a major role in fostering the translational research needed to find effective treatments and/or a cure for children afflicted with HGPS.

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Erratum

In the article ''Reduction in Glutathione Peroxidase 4 Increases Life Span Through Increased Sensitivity to Apoptosis,'' which appeared in the September 2007 issue [*J Gerontol A Biol Sci Med Sci.* 2007;62(9):932–942], author Holly Van Remmen's name should have appeared as ''Holly Van Remmen.''