ideal for gene-replacement therapy. However, in the light of these recent findings, this strategy might have to be re-examined. In addition, DNA-damaging agents used in anti-cancer treatment increase p53 activation and could lead to age-related disorders later on. Thus, the significance of inhibiting drug-induced p53 activation in normal tissues during cancer treatment regimens [15] becomes even more relevant. Clearly, p53 plays a key role in mediating the senescence response of cells to various stimuli. If aging is a response to damage, then individuals with normal p53 levels, who are continually exposed to oncogenic insults (e.g. smoking), might age faster, even if they do not get cancer, because of a high or chronic level of p53 activation.

References

1 Levine, A.J. (1997) p53, the cellular gatekeeper for growth and division. *Cell* 88, 323–331
2 Tyner, S.D. *et al.* (2002) p53-mutant mice that display early ageing-associated phenotypes. *Nature* 415, 45–53
3 Itahana, K. *et al.* (2001) Regulation of cellular senescence by p53. *Eur. J. Biochem.* 268, 2784–2791
4 Campisi, J. (2001) Cellular senescence as a tumor-suppressor mechanism. *Trends Cell Biol.* 11, S27–S31
5 Hollstein, M. *et al.* (1991) p53 mutations in human cancers. *Science* 253, 49–53
6 Levine, A.J. *et al.* (1991) The p53 tumour suppressor gene. *Nature* 351, 453–456
7 Donehower, L.A. *et al.* (1992) Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. *Nature* 356, 215–221
8 Jacks, T. *et al.* (1994) Tumor spectrum analysis in p53-mutant mice. *Curr. Biol.* 4, 1–7
9 Giaccia, A.J. and Kastan, M.B. (1998) The complexity of p53 modulation: emerging patterns from divergent signals. *Genes Dev.* 12, 2973–2983
10 Ko, L.J. and Prives, C. (1996) p53: puzzle and paradigm. *Genes Dev.* 10, 1054–1072
11 Waldman, T. *et al.* (1995) p21 is necessary for the p53-mediated G1 arrest in human cancer cells. *Cancer Res.* 55, 5187–5190
12 Bunz, F. *et al.* (1998) Requirement for p53 and p21 to sustain G2 arrest after DNA damage. *Science* 282, 1497–1501
13 Chang, B.D. *et al.* (2002) Molecular determinants of terminal growth arrest induced in tumor cells by a chemotherapeutic agent. *Proc. Natl. Acad. Sci. U. S. A.* 99, 389–394
14 Martin, L.J. (2001) Neuronal cell death in nervous system development, disease, and injury. *Int. J. Mol. Med.* 7, 455–478
15 Komarov, P.G. *et al.* (1999) A chemical inhibitor of p53 that protects mice from the side effects of cancer therapy. *Science* 285, 1733–1737

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Meeting Report

Searching for clues to premature aging

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In the late 1800s, Hutchinson reported two young boys with 'congenital absence of hair and its appendages'. They, and an additional patient, were described further by Gilford, who proposed the term 'progeria' for this condition [1]. Hutchinson–Gilford Progeria syndrome (HGPS) is a rare developmental disorder affecting most of the organ systems in a manner that mimics, to some extent, features of natural aging but at a markedly accelerated rate [2]. In fact, HGPS has been considered as a prototype of premature aging syndromes, although the degree to which it truly recapitulates innate aging phenomena is still being debated.

HGPS is thought to be a genetic disorder, yet the mode of inheritance, molecular basis and pathogenic mechanisms all remain elusive. To stimulate research on HGPS, in particular, and to extend our understanding of the aging processes, in general, the Massachusetts-based Progeria Research Foundation, jointly with the National Institutes of Health (NIH), organized an unprecedented international workshop on HGPS. The participants were representative of a spectrum of clinical expertise, and researchers from broad areas of molecular, cellular and developmental biology, as well as immunology, endocrinology, geriatrics and genetics, among others, presented their findings on this complex syndrome. The major focus was on the phenotypes of HGPS, with emphasis on the pathology of the extracellular matrix of connective tissue. It was hoped that clues from several organ systems would suggest promising avenues of research for understanding the mechanistic basis of this disease.

A role for hyaluronic acid?

One of the early findings considered as a solid clue to the pathogenic mechanism of HGPS, particularly the cardiovascular involvement, is the reported increase in the urinary hyaluronic acid (HA) [3]. The hypothesis, as presented by Thomas Wight (Hope Heart Institute, Seattle, WA, USA), has been that proteoglycans, and HA in particular, play a prominent role in the formation of vascular lesions by (1) increasing vascular lesion mass and volume; (2) trapping and retaining lipoproteins; and (3) altering the proliferative and migrating phenotype of the cells that regulate the lesion. This hypothesis, in relation to HGPS, now appears to be in considerable doubt. Leslie Gordon, a cell biologist working with Bryan Toole at Tufts University (Boston, MA, USA) and Brown University (Providence, RI, USA) reported her studies on HA in serum and urine in 14 patients with HGPS. Careful analyses, using several independent techniques, showed considerable variation in the HA levels, but, surprisingly, no difference with the age-matched controls or with increasing patient age. Her analyses also showed normal hyaluronidase activity both in the serum and urine, and the sizes of the urinary HA molecules appeared normal. Thus, these latest data do not support the notion that abnormalities in HA are a consistent pathogenic feature in HGPS.

Alterations in collagen and elastin

Clues for the etiology and pathogenic mechanisms of HGPS were also sought by examining several organ systems, including the cardiovascular system, bones and skin. For example, careful

evaluations of bone pathology (Frederic Shapiro, Children's Hospital, Boston, MA, USA), suggested that abnormal bone development and dysplasia, rather than premature bone aging and osteoporosis, accompany this syndrome. The pathology of the cardiovascular lesions appears to be less well defined (Leslie Smoot, Children's Hospital, Boston, MA, USA), and careful comparison of vascular changes in HGPS with typical cardiovascular aging was identified as an area for further research.

Particularly interesting are the observations on early scleroderma-like cutaneous changes, which manifest with uneven thickening of the skin, associated with keloidal lesions and hypertrophic scars (Jouni Uitto, Jefferson Medical College, Philadelphia, PA, USA). Histopathology using special stains has revealed connective tissue deposition in the dermis, particularly accumulation of hyalinized collagen fibers, associated with epidermal atrophy, decreasing adnexal structures, and loss of subcutaneous adipose tissue [4]. These findings, which are similar to those in Werner syndrome, another premature aging syndrome, have some features of scleroderma, a complex acquired, late-onset autoimmune disorder. The etiological considerations for scleroderma have included cytokine factors [particularly transforming growth factor (TGF)-β1], immunological modulation, hypoxia and clonal selection of collagen overproducer cells [5], which could also contribute to dermal fibrosis in HGPS. However, these changes are by no means specific for HGPS and are found in association with several clinical conditions.

Earlier observations have also suggested abnormalities in elastin metabolism, and familial co-segregation of the 'elastin phenotype' in skin fibroblasts has been proposed [6], based on elevated elastin production in skin fibroblast cultures found in patients with HGPS. This 'high elastin producer' phenotype has been suggested to be accompanied by an attenuated response to TGF-β1 and serum, whereas conditioned medium from HGPS fibroblast cultures modulates elastin synthesis in control cells, suggesting the presence of an 'elastogenic factor' [6]. Careful examination of the data reveals, however, that the results are rather inconsistent and limited to a few fibroblast strains from HGPS patients.

Collectively, connective tissue changes can be detected both in the skin and in dermal fibroblast cultures from patients with HGPS, but these findings are neither consistent nor specific for this condition. It is reasonable, therefore, to consider such changes as secondary, possible downstream targets of a mutated gene product with putative regulatory or signaling function.

Molecular genetics of HGPS

The molecular basis of HGPS has remained unknown, and the disease has so far not been correlated with a specific gene. Candidate genes include those involved in DNA repair, but specifically, the *WRN* gene, which encodes a helicase and harbors mutations in Werner syndrome, has been excluded in HGPS [7]. Even the precise mode of inheritance of HGPS is unknown. In support of *de novo* dominant mutations are the observations that the recurrence of the disease in siblings of an affected individual is very rare. Furthermore, there is no excess of consanguinity in families with an affected individual and there is somewhat advanced paternal age (Ted Brown, New York State Institute for Basic Research, Staten Island, NY, USA). A few multiplex families with consanguinity have been reported, but it was argued that these individuals are phenotypically distinct and have a different disease. Nevertheless, as the affected individuals do not reach sexual maturity, the mode of inheritance can be addressed with certainty only after the mutated gene has been identified.

Several groups are at the early stages of developing strategies for gene identification. For example, Francis Collins and his group at the National Human Genome Research Institute (Bethesda, MD, USA) are planning to use homozygosity mapping in search for the gene, with the assumption that HGPS is autosomal recessive, at least in a subset of families. John Sedivy at Brown University (Providence, RI, USA) proposes to clone the HGPS-causing gene by somatic cell complementation, taking advantage of two recent technological developments. The first is identification of differentially expressed genes by expression profiling of HGPS cells compared with normal cells by oligonucleotide microarrays. The second is the development of highly efficient retroviral vector systems that permit the construction of high-complexity cDNA expression libraries and their subsequent screening by infection and phenotypic analysis of mammalian cells in culture.

Considering the small number of affected individuals (estimated at one in 4–8 million births), paucity of multiplex families and lack of obvious karyotypic abnormalities, the gene hunt could be arduous. However, the payoff could be huge, not only to the individuals and families affected with HGPS, but towards improved understanding of aging phenomena, in general, and those affecting the cardiovascular system, in particular.

The driving force behind HGPS research has been The Progeria Research Foundation, currently headed by Audrey Gordon, and committed to finding the cause and eventually treatment and perhaps cure for this devastating disease. 'We are a relatively young organization, yet we believe that we are on the right track as we together strive for that ultimate goal of finding the cure. This meeting will serve as an invaluable resource to our efforts in the foreseeable future,' said Gordon. Indeed, children with HGPS and their families are counting on it.

References

1 DeBusk, F.L. (1972) The Hutchinson–Gilford Progeria Syndrome. *J. Pediatr.* 80, 697–724
2 Martin, G.M. and Oshima, J. (2000) Lessons from human progeroid syndromes. *Nature* 408, 263–266
3 Zebrower, M. *et al.* (1986) Urinary hyaluronic acid elevation in Hutchinson-Gilford Progeria Syndrome. *Mech. Ageing Dev.* 35, 39–46
4 Gillar, P.J. and McCourt, J.W. (1991) Progressive early dermatologic changes in Hutchinson–Gilford Progeria syndrome. *Pediatr. Dermatol.* 8, 199–206
5 Uitto, J. and Kouba, D.J. (2000) Cytokine modulation of extracellular matrix gene expression: Relevance to fibrotic skin diseases. *J. Dermatol. Sci.* 24, S60–S69
6 Giro, M. and Davidson, J.M. (1993) Familial co-segregation of the elastin phenotype in skin fibroblasts from Hutchinson–Gilford Progeria. *Mech. Ageing Dev.* 70, 163–176
7 Oshima, J. *et al.* (1996) No detectable mutations at Werner helicase locus in progeria. *Lancet* 348, 1106

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