

■ MOLECULAR BIOLOGY

Aging, Nuclear Architecture, and Cancer

Scaffidi P and Misteli T. Lamin A-dependent nuclear defects in human aging. *Science* 312: 1059–63, 2006.

Aging is a major cancer risk factor. It is estimated that by the year 2030 more than 70% of new tumors will occur in individuals 65 years and older. Elucidation of the molecular mechanism involved in physiological aging is critical for advancing our understanding of tumor formation. However, studying the human aging process at the molecular level is difficult, and it is rapidly becoming clear that animal models do not provide an adequate picture of human aging. Naturally occurring premature aging diseases are powerful tools to explore human aging and its link to cancer.

Possibly the most dramatic and remarkable premature aging disorder is Hutchinson-Gilford Progeria Syndrome (HGPS). Patients appear normal at birth. However, they experience slow physical development within a few months and rapidly develop typical aging symptoms, including loss of hair, changes to their bone structure, loss of subcutaneous fat, and most importantly, the patients are afflicted by atherosclerosis, which is invariably fatal in their mid-teens.

One of the surprising features of HGPS is its molecular basis. The vast majority of cases are caused by a point mutation in the lamin A/C gene, which encodes two of the major architectural proteins of the cell nucleus, lamins A and C. These proteins, together with B-type lamins and numerous lamin-associated proteins, form the nuclear lamina, an interconnected structural meshwork at the periphery of the cell nucleus thought to be involved in protecting the genome from mechanical stress. The detrimental effect of the disease-causing mutation is brought about by virtue of its activation of a cryptic splice site within exon 11 of the lamin A/C gene, leading to the production of a truncated form of lamin A, referred to as progerin, which appears to disrupt the structure and function of the lamina network (**Figure 1**).

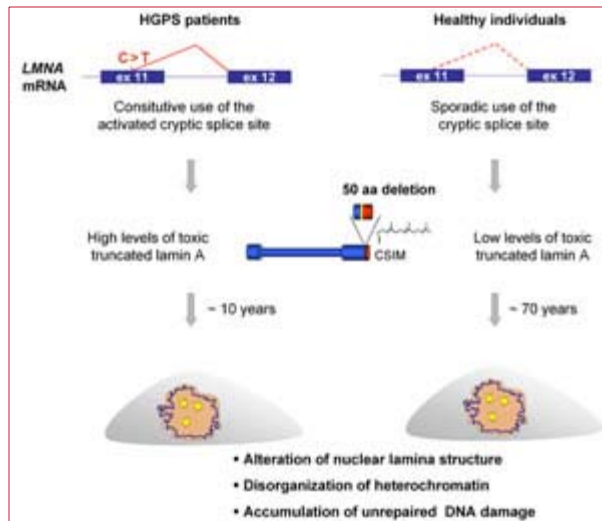


Figure 1. Molecular parallels between premature aging and physiological aging. The premature aging disease Hutchinson-Gilford Progeria Syndrome (HGPS) is caused by activation of a cryptic splice site in the lamin A/C gene (*LMNA*) leading to the production of a dominant-negative lamin A protein isoform. The protein disrupts nuclear function and leads to defects in chromatin organization and DNA repair. During normal aging, the same cryptic splice site in *LMNA* is used at low levels. Although the production of aberrant lamin A is tolerated in young cells, it leads to defects in aged cells similar to those in the cells of HGPS patients. CSIM, C-terminal CAAX motif (C, cysteine; A, usually an aliphatic residue; and X, any amino acid).

Because the major cellular function of lamin A is to establish nuclear architecture, it was not unexpected that HGPS patients have numerous major defects in nuclear structure. Most importantly, HGPS nuclei have aberrant shapes. Also their chromatin is disorganized, and they contain an increased amount of DNA-damage lesions.

Ever since the discovery of lamin A as the cause of a premature aging disease, a lingering question has been whether defects in nuclear architecture and lamin A in particular were also in any way relevant to physiological aging. This was a particularly pertinent issue because HGPS patients do not exhibit some of the typical hallmarks of aging such as dementia or tumor susceptibility, making the classification of HGPS as a premature aging syndrome somewhat uncertain.

We set out to uncover a potential link between lamin A and normal aging, by asking if cells from old individuals show defects in nuclear structure similar to those found in HGPS cells. Sure enough, we found that cells from 75- to 90-year-old individuals had hallmarks of HGPS patients' cells, including disorganized chromatin and increased levels of unrepaired DNA lesions. These simple observations were the first indication that changes in nuclear architecture are related to the aging process.

But are any of these age-related defects due to the same molecular mechanisms that cause HGPS? We found evidence for such a link when analysis of the splicing pattern of the lamin A/C gene revealed that the same cryptic splice site whose activation causes HGPS is also used at low frequency in healthy individuals and leads to the production of low levels of

progerin (Figure 1).

At the time, we hypothesized that the use of the cryptic splice site would increase with age resulting in elevated production of aberrant protein and thus leading to the observed nuclear defects. To our surprise, this was not the case and no accumulation of progerin was found in aged cells. To prove that the production of the aberrant lamin A protein was indeed responsible for the age-related nuclear defects, we took advantage of technology previously developed by us to block the aberrant splicing event in the lamin A/C gene (Scaffidi P and Misteli T. *Nat Med* 11: 440–5, 2005). To do so, we introduced into cells a morpholino oligonucleotide complementary to the aberrant splice site. The oligonucleotide blocks the access of the pre-mRNA splicing machinery to the cryptic splice site and in this way suppresses the production of progerin mRNA and consequently protein. When applied to cells from old individuals, we found that several age-related nuclear defects were reversed and cells had hallmarks of young cells. Based on these observations, we propose that prolonged exposure to low levels of progerin leads to deleterious effects in aged cells (Figure 1).

These experiments have been insightful for two reasons. First, they document a novel mechanism in aging. Lamin A and nuclear architecture are clearly involved in aging, although it is not clear how they act at the molecular level or what kind of cellular age-related responses they trigger. The fact that we can reverse the cellular aging symptoms by elimination of the aberrant lamin A protein is obviously a tantalizing observation. Second, and maybe more importantly, our results establish HGPS as a true aging model. We are particularly interested in this finding because one of the key features of HGPS is the absence of tumors, whereas most other premature aging diseases are characterized by high tumor susceptibility. We are currently exploring whether HGPS will be a useful model system for delineating the molecular links between aging and tumor formation.

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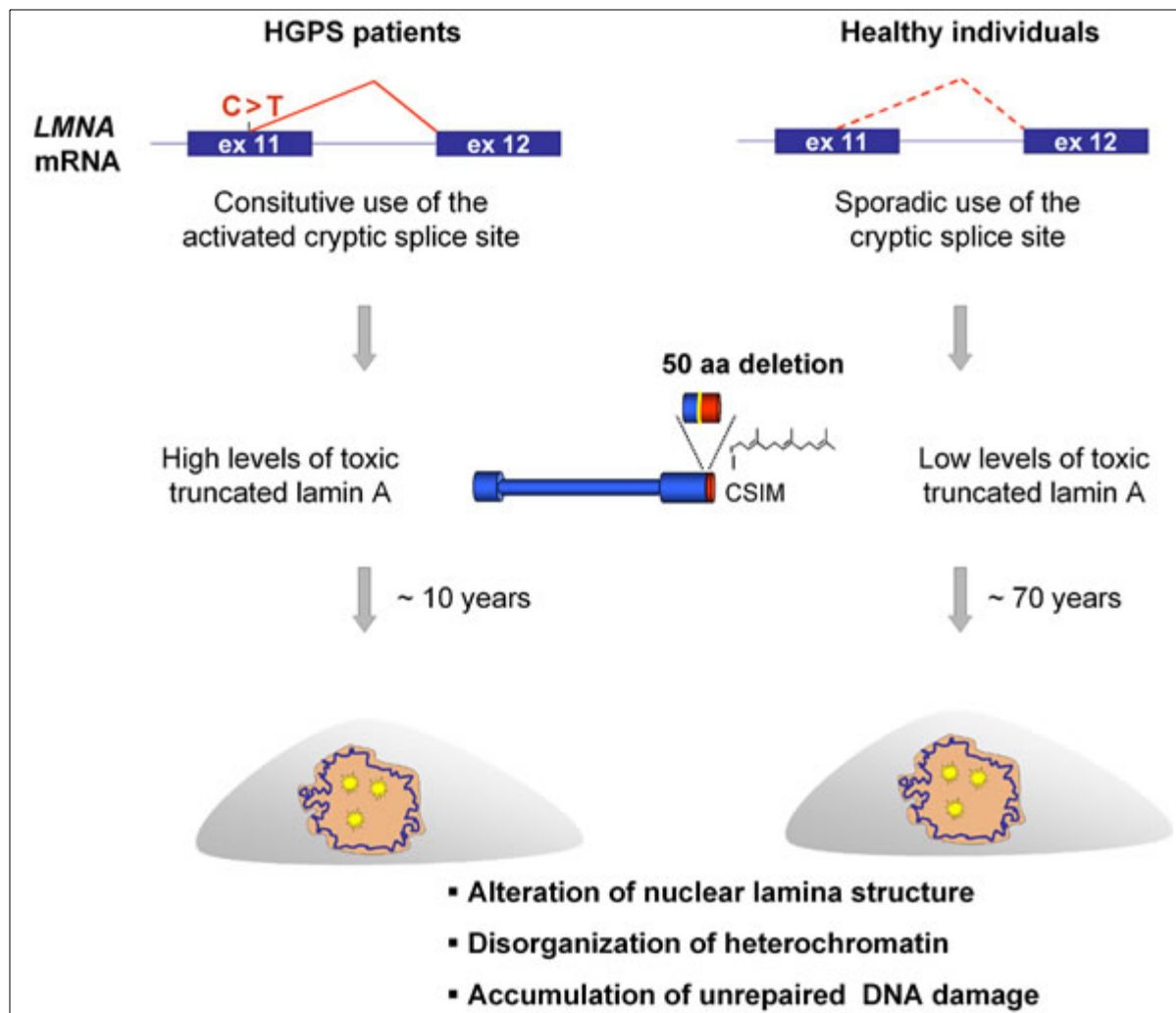


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