AGEING

Age-old quest

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The nuclear lamina, a key structural element of the nucleus, is a scaffold-like network of protein filaments that is comprised of A- and B-type lamins. The premature-ageing disease Hutchinson–Gilford progeria syndrome (HGPS) is caused by a mutation in the gene that encodes lamin-A (*LMNA*). Scaffidi and Misteli therefore questioned how HGPS might relate to normal ageing and whether lamin-A could have a role in this process. They now report in *Science* that HGPS and physiological ageing share a common molecular mechanism.

The authors first examined several skin-fibroblast cell lines from normally aged 81–96-year-old individuals and found that there were nuclear defects that were similar to those seen in HGPS cells, including altered histone-modification patterns in a significant subpopulation of cells. They also found that the nuclear defects — which accumulate in passaged, cultured HGPS cells — accumulate more rapidly in cells from aged donors than from young donors.

The mutation in *LMNA* that causes HGPS leads to the activation of a cryptic splice site and to the aberrant removal of 150 nucleotides at the 3′ end of exon 11. The resulting mRNA (termed Δ150 *LMNA*) generates a lamin-A isoform that lacks 50 amino acids towards its C-terminal end (Δ50 lamin-A). Scaffidi and Misteli found that cells from aged individuals express Δ150 *LMNA* and show aberrantly localized nuclear lamin-A, as is the case in HGPS cells. Strikingly, by blocking the *LMNA* cryptic splice site in cell lines from aged donors, the authors were able to reverse the defects in age-related nuclear structures, which directly shows that the Δ50 lamin-A isoform causes these abnormalities.

Young cells also contain small amounts of Δ50 lamin-A, but Scaffidi and Misteli propose that old cells might be less able to neutralize these aberrant isoforms and that the prolonged presence of these isoforms in the nucleus could lead to the age-related nuclear defects. Of particular interest for future studies is the possibility that interference with lamin-A could modulate the physiological ageing process, perhaps bringing us one step closer in the age-old quest for the fountain of youth.

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