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Delineating the chain of events that trigger cellular senescence in the premature aging syndrome Hutchinson-Gilford progeria

Hutchinson-Gilford Progeria (HGPS) is a premature aging syndrome caused by aberrant splicing of *LMNA* that results in a truncated and permanently farnesylated form of lamin A, called progerin. HGPS patients exhibit characteristics of aging, including alopecia, impaired growth, lipodystrophy, altered pigmentation, bone defects, and die in their mid-teens as a result of cardiovascular complications. Our goal is to elucidate the molecular mechanism that accelerates aging in progeria and understand its relevance to normal aging. On a cellular level, progerin expression causes nuclear abnormalities, perturbed nucleo-cytoplasmic transport, heterochromatin loss, DNA damage, impaired proliferation and premature senescence. Some of these defects can be prevented by ectopic expression of telomerase, or by modulating the DNA damage response specifically at telomeres. What remains unclear is how these different phenotypes are temporally and mechanistically linked, and whether they are a cause, or a consequence of cellular senescence. To address these questions, we used a doxycycline-inducible expression system to introduce different lamin A mutants into human primary and telomerase-immortalized fibroblasts. This system, in conjunction with single-cell immunofluorescence microscopy, enabled us to delineate the temporal chain of events that occurs upon progerin expression across the cell cycle, and ultimately culminates in premature senescence. As perturbations of the nuclear lamina are known to occur during chronological aging, these results provide evidence for a mechanistic link between the nuclear envelope, chromatin structure and telomeres that is disrupted in progeria and possibly normal human aging.