Molecular functions of the nuclear lamina in cell aging & senescence: lessons from Hutchinson-Gilford progeria

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CMX創発医学講演会

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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, skin thinning, altered pigmentation, lipodystrophy, bone defects, and die in their mid-teens due to cardiovascular complications. Our goal is to elucidate the molecular mechanism(s) that accelerate aging in progeria and understand its relevance to normal aging. On a cellular level, progerin expression causes nuclear abnormalities, 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 primary and telomerase-immortalized human 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.