BDR SEMINAR in Kobe

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16:00-17:00, 7F Seminar Room, DB Building A

The role of heterochromatin in the accelerated aging syndrome Hutchinson-Gilford progeria

Summary

Hutchinson-Gilford Progeria (HGPS) is a rare premature aging syndrome, caused by a mutated form of lamin A, called progerin. HGPS patients exhibit signs of premature aging, including alopecia, skin atrophy, aberrant pigmentation and die in their mid-teens due to cardiovascular complications. Our goal is to elucidate the molecular mechanism(s) that trigger premature aging in progeria and to understand whether these findings are relevant to normal aging.

On a cellular level, we and others previously demonstrated that progerin-expression causes DNA damage, heterochromatin loss, impaired proliferation and premature senescence, which are prevented by ectopic expression of telomerase or LAP2alpha (lamina-associated polypeptide 2alpha). However, it remains unclear how progerin causes these disease-associated phenotypes, how they are causally linked – and how both telomerase and LAP2alpha can prevent them. To address these questions, we developed a doxycycline-inducible system to restrict the expression of progerin to specific cell cycle stages. This system, in conjunction with single-cell immunofluorescence microscopy, enabled us to delineate the temporal chain of events that occurs upon progerin-expression and ultimately results in premature senescence. Taken together, our results provide evidence for a mechanistic link between the nuclear lamina, chromatin structure and telomeres that is disrupted in progeria. These findings may be relevant to normal aging as chromatin structure abnormalities and telomeric DNA damage accumulate during chronological aging.

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