AGEING

Heterochromatin disorganization associated with premature ageing

Werner syndrome (also known as adult progeria) is a premature ageing disorder with phenotypes such as grey hair, osteoporosis and diabetes, which are linked to defects in mesodermal tissue. Werner syndrome is caused by mutations in the *WRN* gene, which is involved in several fundamental cellular mechanisms, including DNA replication and repair, as well as telomere maintenance. Zhang *et al.* now report that the WRN protein is also involved in the maintenance of heterochromatin, and that progressive disorganization of heterochromatin underlies the pathology of premature cellular ageing seen in individuals with Werner syndrome.

By using bacterial artificial chromosome recombineering to knock out the region in *WRN* encoding the DNA helicase domain in human embryonic stem (ES) cells, the team were able to generate a $WRN^{-/-}$ ES cell model. Then, to test their hypothesis that the degeneration of mesodermal tissue that is associated with ageing could be linked to a decline in mesenchymal stem (MS) cells, they differentiated the $WRN^{-/-}$ ES cells into MS cells. After serial passaging, the $WRN^{-/-}$ MS cells displayed cellular characteristics of ageing; furthermore, when these cells were transplanted into NOD/SCID (non-obese diabetic/severe combined immunodeficiency) mice, they were eroded more quickly than wild-type cells. indicating that loss of WRN is associated with premature cellular senescence.

Notably, $WRN^{-/-}$ MS cells displayed enlarged nuclei and differences in DNA staining intensity, indicating an altered heterochromatin structure. Moreover, histone H3 lysine 9 trimethylation (H3K9me3), a heterochromatin mark, was found to be substantially downregulated in $WRN^{-/-}$ MS cells and enriched in $WRN^{+/+}$ MS cells in more than 70 consecutive peaks, mostly in subtelomeric or subcentromic regions. Almost 40% of these peaks were not found in $WRN^{-/-}$ MS cells. Centromere packing proteins and nuclear membrane component proteins were the most downregulated genes in $WRN^{-/-}$ MS cells, as shown from RNA sequencing analysis.

Co-immunoprecipitation identified an association of WRN with the heterochromatin proteins SUV39H1 (a histone methyltransferase), HP1α and LAP2β (a heterochromatin anchoring protein), which points to a role for these proteins in the stability of heterochromatin. Interestingly, knockdown of either SUV39H1 or HP1α in $WRN^{+/+}$ MS cells reduced H3K9me3 levels and induced cellular senescence.

Finally, to see whether such heterochromatin disorganization could be a common feature of human stem cell ageing, the team then extracted dental pulp MS cells from 6 young individuals (7–26 years of age) and 6 old individuals (58–72 years of age). Notably, there was a substantial decrease of WRN protein levels, as well as H3K9me3, SUV39H1 and LAP2β levels, in the older individuals, which suggests that a common mechanism might be involved in general physiological ageing.

These results indicate that the disorganization of heterochromatin might be involved in premature pathological ageing, although the development of models of Werner syndrome also has the potential to unlock key features of physiological ageing.

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