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MOBILE ELEMENTS

Putting the brakes on ageing

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A new study in *Drosophila melanogaster* reports that ageing-related changes in heterochromatin lead to the activation of transposable elements (TEs). This activation can be suppressed by dietary, genetic or pharmacological interventions to extend longevity.

In fruitflies, ageing is associated with the loss of repressive heterochromatin integrity, which causes the abnormal activation of gene expression in heterochromatic regions. Previous work has established that heterochromatin is enriched for TEs, which are known to have deleterious effects on the genome when transposed, leading some researchers to postulate a role for TEs in ageing.

To explore this hypothesis further, Wood *et al.* measured the expression of approximately 250 heterochromatic genes in two different tissues from old and young flies using RNA sequencing (RNA-seq). The expression of many genes and TEs (most of which were retrotransposons) was increased in both tissues. Notably, this effect was attenuated under conditions of dietary restriction, which are well known to increase longevity.

The team used a reporter system that expresses green fluorescent protein (GFP) upon insertion of a transposon within a specific locus to assess TE mobilization in ageing. Visual monitoring of flies revealed an increase in the level of TE transposition with ageing, and longer lifespans were associated with later onset of transposition. Similar to TE expression, TE transposition was delayed by dietary restriction.

To assess the causality of the relationship between heterochromatin, ageing and TE transposition, the authors sought to disrupt heterochromatin integrity by genetically manipulating the small interfering RNA (siRNA) and Sir2 pathways, both of which are involved in the maintenance of repressive heterochromatin. To this end, they generated transgenic flies that overexpress genes encoding key factors in these pathways, namely *Sir2*, *Dicer2 and Su(var)1–Su(var)9*, and then assessed TE expression. TEs that displayed the greatest ageing-related increase in expression in wild-type flies were either attenuated or downregulated with ageing in all of these transgenic fly strains. By contrast, in *Dicer2*-null mutant flies, TE expression was increased and this was accompanied by an increase in double-strand DNA breaks, demonstrating the deleterious effects of impaired TE silencing. *Sir2* overexpression had previously been shown to increase longevity; in this study, the authors observed the same effect for all of the genetic manipulations that decreased TE expression.

To determine whether this increased longevity could be directly attributed to TE activity, the authors blocked TE transposition in *Dicer2*-mutant flies (which display high levels of TE activity) by administering the reverse transcriptase inhibitor 3TC. This direct inhibition of TE activity resulted in increased longevity relative to untreated flies.

Together these findings suggest that life-extending pathways that alter heterochromatin increase longevity, at least in part, through the suppression of TE activation. Moreover, they suggest that an age-related breakdown of TE silencing may be a contributing factor to ageing, consistent with the previously proposed retrotransposon theory of ageing.

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ORIGINAL ARTICLE Wood J. G. *et al.* Chromatin-modifying genetic interventions suppress age-associated transposable element activation and extend life span in *Drosophila*. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1604621113 (2016)