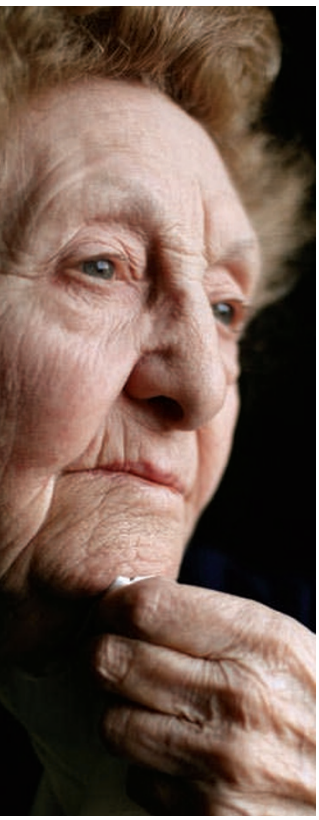
AGEING

A SIRTain role in ageing



Although DNA damage is known to contribute to age-related changes in mammals, the molecular basis of this connection is poorly understood. A study in mice now reveals that the relocalization of a chromatin-modifying protein in response to DNA damage contributes to age-related changed in gene expression.

In *Saccharomyces cerevisiae*, the silencing of genes at mating-type loci by the histone deacetylase Sir2 is reversed during DNA damage and ageing when Sir2 relocalizes to areas of genomic instability. Sinclair and colleagues show that the mammalian Sir2 orthologue, sirtuin 1 (SIRT1), acts in a similar way. Using mouse embryonic stem cells, the authors found that SIRT1 normally associates with major satellite repeats and a large number of promoters of protein-coding genes. However, when cells were subjected to stress (H_2O_2 or methyl methanesulphonate treatment), SIRT1 dissociated from these sites and redistributed to random promoters. Following H_2O_2 treatment, this redistribution was correlated with increased acetylation at lysine 26 of histone H1 and with increased transcription from SIRT1-associated promoters and repeats.

Because yeast Sir2 relocates to sites of DNA repair, the authors asked whether SIRT1 has a role in the response to stress-induced DNA repair in mouse cells. Indeed, reducing SIRT1 activity through RNAi or through chemical inhibitors compromised the normal response to double-stranded breaks (DSBs) and resulted in increased numbers of chromosome fusions. Furthermore, overexpression of SIRT1 in lymphocytes of mice that are heterozygous for the tumour suppressor gene *Trp53* led to a reduced incidence of tumours and increased survival following exposure to gamma irradiation.

Next, the authors compared transcriptional derepression following oxidative stress with the well-characterized age-related changes in gene expression that take place in the neocortex of the mouse brain. More than two-thirds of the genes derepressed by oxidative stress were also derepressed during ageing. Providing *in vivo* evidence that SIRT1 function affects ageing-related expression, brain-specific overexpression of SIRT1 in transgenic mice completely suppressed the transcriptional derepression at sites of SIRT1 binding that is seen in aged mice.

Although the SIRT1-related transcriptional changes caused by stress are a beneficial response to cellular damage, the authors hypothesize that over time the constitutive triggering of the SIRT1 response might cause permanent changes to the structure of chromatin at sites of DSB repair, leading to changes in gene expression that contribute to ageing.

Elizabeth Neame

ORIGINAL RESEARCH PAPER Oberdoerffer, P. *et al.* SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during ageing. *Cell* **135**, 907–918 (2008)