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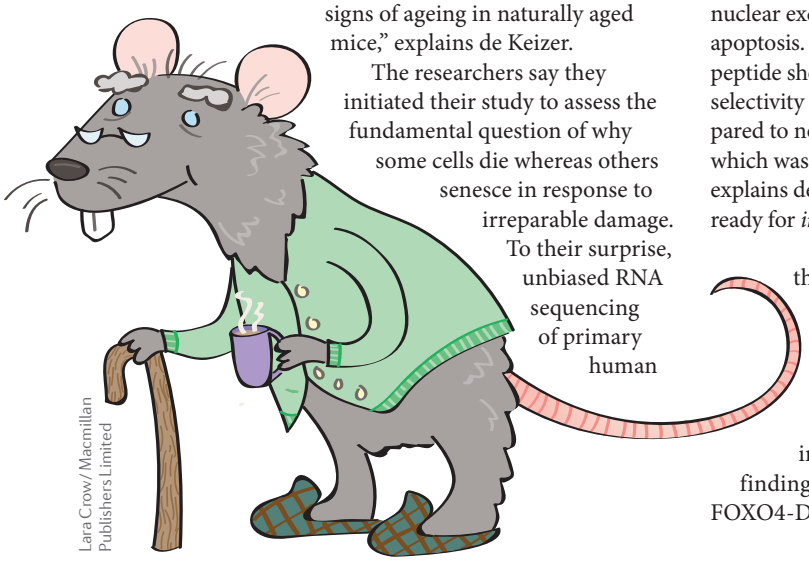
AGEING

Targeting senescence-associated tissue damage

> “Targeting FOXO4 signalling … restores renal function in rapidly ageing and naturally aged mice”



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Cellular senescence — an irreversible fate in which cells become permanently withdrawn from the cell cycle — can be induced by a variety of stressors. Although the induction of cellular senescence can be beneficial in the acute setting, chronic accumulation of senescent cells can impair tissue function and drive features of ageing, suggesting that approaches to stimulate apoptosis and clearance of senescent cells might delay age-related disease and counteract tissue deterioration. In a new study, Peter de Keizer and colleagues identify FOXO4 as a key regulator of senescent cell viability, and demonstrate that targeting FOXO4 signalling causes apoptosis and restores renal function in rapidly ageing and naturally aged mice. “The finding that our FOXO4-DRI peptide restores fitness and kidney function in naturally aged mice was especially exciting, as to our knowledge there aren’t many reports showing that it is possible to reverse signs of ageing in naturally aged mice,” explains de Keizer.

The researchers say they initiated their study to assess the fundamental question of why some cells die whereas others senesce in response to irreparable damage. To their surprise, unbiased RNA sequencing of primary human IMR90 fibroblasts showed upregulation of pro-apoptotic factors in fibroblasts induced to senesce by exposure to ionizing radiation, suggesting that despite the presence of apoptotic machinery, execution of the death programme is restrained in senescent cells. “We then identified the transcription factor FOXO4 as pivotal in maintaining senescent cell viability, indicating that inhibition of FOXO4 signalling might enable the removal of these cells and counteract the loss of tissue homeostasis caused by tissue damage or ageing,” says de Keizer.

Further studies demonstrated that FOXO4 forms a complex with the pro-apoptotic factor p53 in senescent cells, prompting de Keizer and colleagues to design a cell-permeable peptide that comprised part of the p53-interaction domain in FOXO4 in D-retro-inverso (DRI) conformation, to interfere with FOXO4–p53 binding. In senescent cells, inhibition of FOXO4–p53 binding led to p53 nuclear exclusion and cell-intrinsic apoptosis. “This FOXO4-DRI peptide showed greater than 10-fold selectivity in killing senescent compared to non-senescent fibroblasts, which was our first eureka moment,” explains de Keizer. “We were then ready for *in vivo* translation.”

To assess the effects of the FOXO4-DRI peptide in senescence-related pathologies, the researchers first studied its effects in mice with doxorubicin-induced liver damage, finding that administration of FOXO4-DRI reduced the viability of senescent cells and attenuated doxorubicin-induced liver damage. The researchers next assessed whether inhibition of FOXO4 signalling could counteract age-induced tissue damage, using $Xpd^{TTD/TTD}$ mice — a model based on the human premature ageing syndrome trichothiodystrophy. These mice are characterized by a rapid ageing phenotype, with accelerated senescence and early-onset kidney damage as assessed by plasma urea levels. Interestingly, the FOXO4-DRI peptide led to reduced indices of renal senescence, increased apoptosis and normalized tubular IL-6 expression and plasma urea levels. Similar effects on renal function were observed in naturally aged mice, suggesting that FOXO4-DRI can restore kidney homeostasis by targeting senescent cells in the ageing kidney.

De Keizer states that his main priority at this stage is to further assess the safety of the FOXO4-DRI peptide *in vivo*. “This compound eliminates cells; undesirable cells, but cells nonetheless,” he says. “Once we have a better understanding of the safety of this compound, we would like to assess its use in patients suffering from severe diseases, such as late-stage cancer, in which toxicity might be less of an issue than in patients with milder disease and in those with age-related tissue damage.”

Susan J. Allison

ORIGINAL ARTICLE Baar, M. P. *et al.* Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. *Cell* **169,** 132–147 (2017).
FURTHER READING Sturmlechner, I. *et al.* Cellular senescence in renal ageing and disease. *Nat. Rev. Nephrol.* **13,** 77–89 (2017).