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AGEING

Anti-ageing formula

> “accumulation of p16^{INK4A}-positive senescent cells is associated with functional impairment of vital organs”

Philip Patenall/NPG

Cellular senescence — a permanent state of growth arrest — has been associated with a range of age-related diseases. Baker *et al.* now confirm that the accumulation of senescent cells during the normal ageing process is involved in the age-related deterioration of several organs and that the removal of these senescent cells can prolong healthspan.

The authors used a transgenic mouse model (referred to as *ATTAC* mice) in which both GFP and a fusion protein of FK506-binding protein and caspase 8 (FKBP–CASP8) are expressed under the control of a minimal *Ink4a* promoter. In cells that express p16^{INK4A}, which is a hallmark of most senescent cells, administration of the drug AP20187 activates FKBP–CASP8 and triggers cell death. For example, in the white adipose tissue of 12-month-old *ATTAC* mice, GFP-positive cells are positive for a panel of senescence-associated markers, including β-galactosidase, and treatment of these mice bi-weekly with AP20187 from 12 until 18 months of age prevented the accumulation of these senescent cells. The expression of *Ink4a*, *Fkbp–Casp8*, GFP and senescence markers increased between 12 and 18 months in untreated *ATTAC* mice for a range of tissues examined — skeletal muscle, eye, kidney, lung, heart, liver, colon and spleen — and this increase could be attenuated by treatment with AP20187 in all tissues except colon and liver. Thus, the *ATTAC* model can be used to effectively eliminate a large proportion of senescent cells.

On two different genetic backgrounds, for both sexes and for mice fed both high fat (9%) and standard fat (5%) diets, the median lifespans of *ATTAC* mice were increased by 24–27% as a result of twice-weekly treatment with AP20187 from 12 months of age. To assess the impact of senescent cell removal by AP20187 on age-related organ disease, the authors focused on kidney and heart. Treatment of *ATTAC* mice with AP20187 markedly reduced age-related glomerulosclerosis and the associated increase in blood urea nitrogen levels, which indicates preservation of kidney function. AP20187 also prevented the age-related increase in mRNA levels of angiotensin receptor 1a (*Agtr1a*) in the kidney, which is thought to drive sclerosis. In the heart, AP20187 attenuated the age-related reduction in expression of SUR2A, a regulatory subunit of ATP-sensitive potassium channels, which suggests that it preserves cardiac stress tolerance. Indeed, AP20187-treated mice were protected against the age-related hastening of death in response to cardiac stress.

In conclusion, the accumulation of p16^{INK4A}-positive senescent cells is associated with functional impairment of vital organs such as heart and kidney, and their removal after middle age (12 months in mice) can improve health and extend lifespan. In terms of translating these findings to human ageing, it is worth noting that senescent cells also have beneficial effects in tissue repair and in preventing the proliferation of preneoplastic cells, although this study found no evidence of increased fibrosis or cancer development after removal of senescent cells.

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