AGEING

# Balancing self-renewal and ageing

Mammalian ageing has been associated with reduced regenerative capacity. Three new studies now provide a potential link between the tumour suppressor $p16^{INK4a}$, the replicative capacity of stem cells and regenerative capacity in ageing tissues.

Expression of $p16^{INK4a}$ increases with age, and increased $p16^{INK4a}$ expression has been associated with cellular senescence and has been postulated to contribute to ageing. However, whether increased $p16^{INK4a}$ expression functionally contributes to ageing by causing a decline in stem-cell function *in vivo* remained unclear.

Krishnamurthy *et al.* assessed the impact of $p16^{INK4a}$ deficiency and overexpression in pancreatic-islet proliferation. The authors induced $p16^{INK4a}$ expression (to a level similar to that observed in old mice) in young transgenic mice that harboured an extra copy of the $p16^{INK4a}$ gene. These transgenic animals had reduced islet proliferation compared with controls, which prompted the authors to propose that increased levels of $p16^{INK4a}$ in old animals inhibit islet proliferation. Further analysis showed that the loss of $p16^{INK4a}$ did not alter islet proliferation in young mice, but did rescue the age-induced decrease in proliferation.

Because the tumour-prone nature of $p16^{INK4a}$-deficient animals limited the functional studies that could be carried out, Krishnamurthy *et al.* used a model of islet regeneration. Prolonged survival after a single, diabetes-causing treatment with a β-cell toxin requires the regeneration of significant numbers of functional β-cells. Animals that were deficient in $p16^{INK4a}$ exhibited enhanced survival. The greatest differences in survival were observed in the oldest mice, which indicates that $p16^{INK4a}$ mediates a decline in the replicative capacity of islets that is associated with ageing.

Molofsky *et al.* observed increased $p16^{INK4a}$ expression with age in neural progenitors, which prompted them to examine the percentage of progenitors, proliferation and neurogenesis in the forebrain lateral ventricle subventricular zone (SVZ) in young and old $p16^{INK4a}$-deficient mice. The percentage of stem cells, their potential to self-renew and the overall proliferation rate all decline with age in the SVZ. Loss of $p16^{INK4a}$ rescued the age-related decline in cells that can form stem-cell colonies in culture, and partially rescued the overall decline in SVZ proliferation and neurogenesis. The authors proposed that $p16^{INK4a}$ expression could be developmentally programmed to increase with age in order to counter the increasing incidence of cancer in the ageing nervous system. Alternatively, increased $p16^{INK4a}$ expression might reflect the induction of senescence in the ageing cells in response to damage that accumulates with age.

In a third report, Janzen *et al.* showed that $p16^{INK4a}$ expression increased with age in haematopoietic stem cells (HSCs). Studies of differentiation and homing capacity in $p16^{INK4a}$-deficient mice indicated that the age-associated increase in $p16^{INK4a}$ expression restricts the number of HSCs. Further analysis of cell proliferation in young and old wild-type and $p16^{INK4a}$-knockout mice showed no differences in young animals. However, old $p16^{INK4a}$-deficient mice had higher numbers of stem-cells and increased stem-cell function, which was associated with increased proliferation.

What is the mechanism of $p16^{INK4a}$ function? Based on the analysis of markers that have been associated with stem-cell self-renewal, such as *Bmi1* and *Hes1*, Janzen *et al.* proposed the following model: in aged animals, the increase in $p16^{INK4a}$ expression is associated with a reduced repopulating capacity and decreased expression of *Hes1*, whereas $p16^{INK4a}$ deletion is accompanied by an improved repopulating capacity of stem cells and increased expression of *Hes1*.

Taken together, these results from diverse tissues indicate that $p16^{INK4a}$ contributes to mammalian ageing by limiting the self-renewal of regenerative cells — at least in the bone marrow, endocrine pancreas and brain. Whether the balance between self-renewal and ageing is also controlled by $p16^{INK4a}$ in other tissues remains to be investigated.

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> “…$p16^{INK4a}$ contributes to mammalian ageing by limiting the self-renewal of regenerative cells…”

**ORIGINAL RESEARCH PAPERS** Krishnamurthy, J. *et al.* $p16^{INK4a}$ induces an age-dependent decline in islet regenerative potential. *Nature* 6 Sep 2006 (doi:10.1038/nature05092) | Molofsky, A.V. *et al.* Increasing $p16^{INK4a}$ expression decreases forebrain progenitors and neurogenesis during ageing. *Nature* 6 Sep 2006 (doi:10.1038/nature05091) | Janzen, V. *et al.* Stem-cell ageing modified by the cyclin-dependent kinase inhibitor $p16^{INK4a}$. *Nature* 6 Sep 2006 (doi:10.1038/nature05159)