# HIGHLIGHTS



AGEING

## Absence makes the mouse live longer

So far, the only effective way for you to live longer has been to restrict your calorific intake. But a report by Holzenberger and colleagues in *Nature* might offer another potential way — knocking out the insulin-like growth factor type 1 receptor (IGF1R) in mice increased their lifespan, indicating that IGF1R could be a crucial regulator of longevity in mammals.

Inactivating the fruitfly insulin-like receptor (*InR*) or the nematode *daf-2* gene, both of which encode components of the insulin or insulin-like signalling pathway, increases the lifespan of these organisms. In a bid to discover whether the IGF1R might control vertebrate longevity, the authors inactivated the *Igf1r* gene by homologous recombination; previous reports had hinted that decreased circulating IGF1 levels were correlated with longevity.

As homozygous-null mutants died at birth, subsequent studies focused on $Igf1r^{+/-}$ heterozygotes, which had half the amount of functional IGF1R protein. $Igf1r^{+/-}$ mice weighed the same as their wild-type counterparts at birth and for the first three weeks. There was a small decrease in the growth of $Igf1r^{+/-}$ mice, although this was only significant in male mice. Most apparent was that, on average, $Igf1r^{+/-}$ mice lived 26% longer than control mice — females lived 33% longer, whereas the increase in males was only 16%.

To discover what mediated this longevity, the authors studied various factors, from body temperature to circadian activity profiles, as metabolism might be important in ageing. No differences were found. Moreover, $Igf1r^{+/-}$ mice were as fertile as their control littermates. Both sets of mice also had the same food uptake, dismissing the possibility that the $Igf1r^{+/-}$ mice lived longer because they restricted their calorific intake.

So what might be responsible for the difference in longevity? Enhanced resistance to oxidative stress was a strong possibility, and it indeed turned out that $Igf1r^{+/-}$ mice, and mouse embryonic fibroblasts derived from them, were more resistant to oxidative stress than controls. At the molecular level, insulin receptor substrate 1 (IRS1) and the p52 and p66 isoforms of Shc, both main substrates of IGF1R, showed decreased tyrosine phosphorylation. p66 Shc mediates cellular responses to oxidative stress, providing a putative mechanism linking IGF1R and oxidative stress. Further analysis showed that two main pathways — the extracellular-signal regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K)–Akt pathway — were down-regulated in $Igf1r^{+/-}$ mice.

So this study has extended the initial findings from non-vertebrates to higher vertebrates — that insulin-like signalling and longevity are linked. Not only are further studies into the sex differences in lifespan needed, but future research needs to investigate potential links between calorific restriction, insulin-like signalling and oxidative stress in longevity.

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### References and links

**ORIGINAL RESEARCH PAPER** Holzenberger, M. *et al.* IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. *Nature* 2002 December 4 (DOI: 10.1038/nature01298)

**FURTHER READING** Gems, D. & Partridge, L. Insulin/IGF signalling and ageing: seeing the bigger picture. *Curr. Opin. Genet. Dev.* **11**, 287–292 (2001)