DOI:
10.1038/nrm2252

IN BRIEF

AGEING

Quantitative mass spectrometry identifies insulin signaling targets in *C. elegans*.

Dong, M.-Q. *et al. Science* **317**, 660–663 (2007)

The homologue of the insulin-like growth factor receptor in *Caenorhabditis elegans*, DAF-2, negatively regulates DAF-16, a class O forkhead box transcription factor, and *daf-2* mutants exhibit extended lifespan. John Yates and colleagues used quantitative mass spectrometry (qMS) to identify proteins that are involved in this anti-ageing signalling network. By labelling proteins in *daf-2* mutants with ^{15}N and comparing the levels with those in wild-type worms (labelled with ^{14}N) by qMS, they identified 86 proteins that could be important. Several of these were validated using RNA interference, identifying key pathways that confer and limit longevity in *daf-2* mutants. Although only 10% of the worm proteome was analysed because of technical limitations, this approach could significantly improve our understanding of signalling networks, including those associated with longevity.

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Type 5 adenylyl cyclase disruption increases longevity and protects against stress.

Yan, L. *et al. Cell* **130**, 247–258 (2007)

Adenylyl cyclase-5 (ADCY5) is mostly expressed in the heart and brain and functions in the β-adrenergic receptor signalling pathway to produce cyclic AMP, which activates protein kinase A (PKA). Stephen Vatner and colleagues showed that *Adcy5*$^{-/-}$ mice have an increased (~30%) median lifespan and a reduction in ageing phenotypes, such as reduced bone density and cardiomyopathy, compared with wild-type mice. Cells from *Adcy5*$^{-/-}$ mice were also more resistant to oxidative stress, which was associated with increased activation of extracellular signal-regulated kinase (ERK), which mediates antioxidative, anti-apoptotic and cell-survival responses. They propose that ERK could become activated in *Adcy5*$^{-/-}$ mice owing to the reduced activity of PKA, which inhibits Raf (an upstream activator of ERK), providing a possible mechanism for the extended lifespan of *Adcy5*$^{-/-}$ mice.

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Sirtuin 2 inhibitors rescue α-synuclein-mediated toxicity in models of Parkinson's disease.

Outeiro, T. F. *et al. Science* **317**, 516–519 (2007)

The risk of developing neurodegenerative diseases, such as Parkinson's disease, increases with age. Therefore, targeting molecular pathways that underlie the ageing process might temper, and possibly prevent, the progression of neurodegeneration. Parkinson's disease is associated with the loss of dopaminergic neurons that contain toxic inclusion bodies (Lewy bodies), which are abnormal, spherical aggregates of protein. Aleksey Kazantsev and colleagues showed that inhibition of sirtuin-2 (SIRT2) — a member of the sirtuin family of histone deacetylases that are associated with cell survival and responses to caloric restriction — significantly reduces the toxicity of Lewy body formation by inducing inclusion body enlargement, thereby reducing their total surface area and aberrant interactions with cellular proteins. This indicates that inhibitors of SIRT2 could delay neurodegeneration and that SIRT2 might have more profound effects on ageing-associated diseases than acknowledged previously.