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Journal club

SIRTUINS AND CALORIE RESTRICTION

Calorie restriction (CR) is by far the most robust intervention, genetic or environmental, for slowing down ageing in mammals. The identification of sirtuins as NAD-dependent protein deacetylases led to the proposal that they mediate the health benefits of CR (Guarente, 2000). However, studies in lower organisms have spawned conflicting reports on the importance of sirtuins in CR.

It was therefore clarifying to read the paper by Someya *et al.* showing that in mice the mitochondrial sirtuin SIRT3 has a central role in CR-mediated protection from a malady of ageing we can all relate to, hearing loss. Mice undergo hearing loss by 12 months of age owing to cumulative oxidative damage to neurons in the inner ear. CR completely protected against this loss in wild-type mice; however, *Sirt3*-knockout mice were unaffected by CR and suffered the same degree of hearing loss as mice on an *ad libitum* (or normal) diet. It is noteworthy that *Sirt3*-knockout mice are so overtly normal that my own laboratory decided not to work on them (a painful lesson against judging a book by its cover). Someya *et al.* satisfyingly link major threads running through ageing research since the 1950s: oxidative damage in mitochondria as a cause of ageing; and CR and sirtuins as palliatives.

> “SIRT3 has a central role in CR-mediated protection from … hearing loss”

What about the nuclear sirtuins, such as SIRT1? Although SIRT1 has a clear role in metabolism, determining its role in ageing has been difficult because of the pleiotropic effects of knocking out *Sirt1*. Fortunately, tissue-specific knockout of *Sirt1* has demonstrated a requirement for this sirtuin in mediating the effects of CR on physiology and stress tolerance (Kume *et al.*, 2010; Schenk *et al.*, 2011).

So, it seems that, at least in mice, sirtuins do mediate some of the effects of CR. But are they required for the CR-mediated extension of lifespan? Although there is evidence consistent with this for SIRT1, to decisively answer this question it will be crucial to determine whether loss of function of each of the seven mammalian sirtuins individually will prevent lifespan extension by CR, and whether overexpression can extend lifespan in normally fed mice. Stay tuned.

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The author declares competing financial interests

ORIGINAL RESEARCH PAPERS Guarente, L. Sir2 links chromatin silencing, metabolism, and aging. *Genes Dev.* **14**, 1021–1026 (2000) | Someya, S. *et al.* Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. *Cell* **143**, 802–812 (2010) | Kume, S. *et al.* Calorie restriction enhances cell adaptation to hypoxia through Sirt1-dependent mitochondrial autophagy in mouse aged kidney. *J. Clin. Invest.* **120**, 1043–1055 (2010) | Schenk, S. *et al.* Sirt1 enhances skeletal muscle insulin sensitivity in mice during caloric restriction. *J. Clin. Invest.* **121**, 4281–4288 (2011)

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