EMBO reports

opinion

Sirtuins and ageing—new findings

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Calorie (or dietary) restriction was first shown to extend rodent lifespan almost 80 years ago, and remains the most robust longevity-promoting intervention in mammals, genetic or dietary. Sirtuins are NAD-dependent deacylases homologous to yeast Sir2p and were first shown to extend replicative lifespan in budding yeast [1]. Because of their NAD requirement, sirtuins were proposed as mediators of the anti-ageing effects of calorie restriction [1]. Indeed, many studies in yeast, *Caenorhabditis elegans*, *Drosophila melanogaster* and mice have supported these ideas [2]. However, a 2011 paper posed a challenge: transgenic strains of *C. elegans* and *Drosophila* that overexpress SIR2 were found not to be long-lived [3].

Rather than review the extensive sirtuin literature previous to that paper, I focus on a few key studies that have followed it, which underscore a conserved role of sirtuins in slowing ageing. In the first study, two highly divergent budding yeast strains—a lab strain and a clinical isolate—were crossed. A genome-wide quantitative trait locus analysis was then performed to map genes that determine differences in replicative lifespan [4]. The top hit was *SIR2*, explaining more than one-half of the difference in replicative lifespan between the two strains (due to five codon differences between the *SIR2* alleles). In *Drosophila*, overexpression of dSIR2 in the fat body extended the lifespan of flies on the normal diet, whereas deletion of *dSIR2* in the fat body abolished the extension of lifespan by a calorie-restriction-like protocol [5]. This example illustrates the key role of *dSIR2* in lifespan determination and its central role in mediating dietary effects on longevity, discussed further below. Another study showed that two transgenic mouse lines that overexpress the mammalian SIRT6—mammals have seven sirtuins—had significantly extended lifespans [6]. Finally, a recent study clearly showed that worm *sir2.1* could extend lifespan by regulating two distinct longevity pathways involving insulin-like signalling and the mitochondrial unfolded protein response [7]. All told, this body of work supports the original proposal that sirtuins are conserved mediators of longevity.

Many other studies also illustrate that sirtuins can mediate the effects of diet. As an example, calorie restriction completely protected against ageing-induced hearing loss in wild type but not *SIRT3*$^{-/-}$ mice [8]. The mitochondrial sirtuin SIRT3 thus helps to protect the neurons of the inner ear against oxidative damage during calorie restriction. Of course, these studies do not imply that sirtuins are the only mediators of calorie restriction effects, but they do indicate that they must be central components.

Finally, what about the translational potential of this research, namely using putative SIRT1-activating compounds—resveratrol and newer, synthetic STACs? Two new studies provide strong evidence that the effects of these compounds really do occur through SIRT1. First, acute deletion of SIRT1 in adult mice prevented many of the physiological effects of resveratrol and other STACs [9]. Second, a single mutation adjacent to the SIRT1 catalytic domain abolished the ability of STACs to activate the enzyme *in vitro*, or to promote the canonical physiological changes *in vivo* [10].

In summary, sirtuins seem to represent a promising avenue by which orally available drugs might deliver anti-ageing benefits normally triggered by calorie restriction. Indeed, the biology of sirtuins is complex and diverse, but this is an indication of their deep reach into key disease processes. Connections between sirtuins and cancer metabolism are but one new example of this. The future path of discovery promises to be exciting and might lead to new drugs that maintain robust health.

CONFLICT OF INTEREST

L.G. is on the Scientific Advisory Board of GlaxoSmithKline.

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EMBO *reports* (2013) **14,** 750; published online 9 August 2013; doi:10.1038/embor.2013.121