Sirtuin to the rescue: SIRT2 extends life span of BubR1 mice
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Why and how we age remains a topic that has kept molecular biologists busy for the past few decades. In recent years, several studies pointed to sirtuins as important players in lifespan regulation, yet, in vivo proof for most of the mammalian homologs was missing. In this issue of The EMBO Journal, Sinclair and colleagues provide novel evidence that SIRT2 is indeed a critical modulator of aging in vivo.

See also: BJ North et al (July 2014)

Organismal aging is associated with a decline of cellular function in tissues, leading to the so-called age-related diseases, including cardiovascular and metabolic diseases, neurodegeneration and cancer (Cosentino & Mostoslavsky, 2013). The molecular mechanisms leading to aging are not yet fully understood and neither is why and how we age remains a topic that has kept molecular biologists busy for the past few decades. In recent years, several studies pointed to sirtuins as important players in lifespan regulation, yet, in vivo proof for most of the mammalian homologs was missing. In this issue of The EMBO Journal, Sinclair and colleagues provide novel evidence that SIRT2 is indeed a critical modulator of aging in vivo.

SIRT2 is a mitotic checkpoint kinase. Previous studies have shown that SIRT2 levels decrease with age (Baker et al., 2004; Humbert et al., 2007; Matsumoto et al., 2007), and overexpression of SIRT2 in vivo extends life span (Baker et al., 2013). The authors start their study presenting molecular evidence convincingly connecting SIRT2 and Sirt2. The authors show that reducing SIRT2 activity or levels diminishes BubR1 protein levels. In a biochemical tour de force, they describe BubR1 as a novel deacetylation target of SIRT2. Using a combination of biochemistry and mass spectrometry analysis, they identified that BubR1 is acetylated specifically by CBP on lysine 668, and this acetylation primes the protein for ubiquitination and subsequent degradation. By deacetylating K668, the authors showed that SIRT2 stabilizes BubR1.

In the second part of the study, North and colleagues presented in vivo studies to provide physiological significance for their findings. Using a transgenic SIRT2 mouse strain (SIRT2tg) crossed with the hypomorphic BubR1 mice (BubR1H/H), they found that SIRT2tg/BubR1H/H mice remained as small as the BubR1H/H; however, they observed a striking 58% increase (122% for male mice) in the median life span and a 21% increase in maximal life span compared to BubR1H/H mice.

North et al. then investigated how SIRT2 rescues BubR1H/H mice. BubR1 mice die of cardiac dysfunction, and indeed SIRT2 does improve cardiac function in male mice. The observation that male mice are more prone than female ones to cardiac dysfunction (Du, 2004) might at least in part explain why SIRT2 is more effective in increasing life span of male mice. It is important to notice that BubR1H/H mice do not show any gender bias (Baker et al., 2004). Moreover, as discussed below, BubR1 mutations are part of an autosomal disease (Wijmenga et al., 2012); therefore, the reason behind this sexual dimorphism remains to be fully understood. As mentioned above, SIRT6 also exhibited sexual dimorphism with regard to lifespan benefits; therefore, it will be interesting to determine whether there is a common mechanism behind such effects.

It is worth noting that SIRT2 fails to fully restore wild-type levels of BubR1, and in fact, the mice hypomorphic for BubR1 and overexpressing SIRT2 still present some of the progeroid phenotypes (e.g., lordokyphosis, cataract, and small size). The authors propose that there is a critical threshold for the levels of BubR1 that is tissue specific, so the amount of protein reached in the heart is sufficient to improve the cardiac function (and life span), but not so in other tissues. In this context, it remains to be tested whether heart, compared to other tissues, exhibits more senescent cells during aging, a possibility that could explain this phenotype. Based on these results, the authors also concluded that there must be other factors regulating BubR1 levels. It will be essential...
to identify these other factors, in order to obtain a full picture on how this key lifespan factor is regulated.

Considering that SIRT2 overexpression increases BubR1 levels also in wild-type MEFs and that aging is accompanied by a decrease of BubR1, we may predict that SIRT2 overexpression would increase lifespan also in wild-type mice, as SIRT6 and SIRT1 do, a possibility that remains to be tested. Although the potential therapeutic benefits of activating SIRT2 in the context of aging will require further studies, the finding by North et al could already find a clinical readout in the treatment of patients affected by mosaic variegated aneuploidy (MVA). MVA is a rare recessive disorder due to BubR1 mutations (Wijshake et al, 2012). Children affected by this disease are cancer prone, exhibit a progeroid phenotype, and die at an early age. In that context, increasing levels of BubR1 in those patients by means of increasing SIRT2 activity could provide an alternative therapeutic possibility.

This study opens other intriguing questions. BubR1 levels decreased with age, yet no data suggest that SIRT2 levels change with age as well. In that regard, rather than sirtuin levels to being affected, it is possible that availability of the cofactor NAD may change with age, in turn affecting SIRT2 activity instead of levels. Indeed, two recent studies provided strong evidence for such a case (Gomes et al, 2013; Stein & Imai, 2014). Although treatments with NAD precursors (NMN, NR) have been proposed to improve healthspan through SIRT1, this new study indicates SIRT2 as another strong candidate behind the beneficial effects of these small molecules. Undoubtedly, North et al shed new light into our understanding of aging and age-related diseases, while setting ground for interesting future studies.

Conflict of interest
The authors declare that they have no conflict of interest.

References


