The Ongoing Saga of Sirtuins and Aging

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Sirtuins are known to slow aging in simple eukaryotes; however, viewing mammalian sirtuins as antiaging proteins may be overly simplistic. In this issue of *Cell Metabolism*, Li et al. (2008) provide evidence that SirT1 has properties consistent with both pro- and antiaging functions in mice.

Sirtuins are a family of NAD-dependent protein deacetylases and ADP ribosyltransferases homologous to the yeast silent information regulator (SIR) 2 (Haigis and Guarente, 2006; Longo and Kennedy, 2006). Over the past decade, sirtuins have gone from a relatively uncharacterized family of yeast proteins to some of the most studied—and certainly the most touted—targets of aging-related research. Sirtuins are generally thought of as prolongevity factors, based on the observation that increased expression of Sir2 orthologs is sufficient to increase life span in yeast, worms, and flies (Guarente and Picard, 2005). It remains unknown, however, whether the mammalian Sir2 ortholog, SirT1, has a similar longevity-promoting role. In this issue, Li et al. examine effects resulting from inhibition of SirT1. Surprisingly, they find that, although life span is shortened, inhibition of SirT1 also leads to cellular phenotypes suggesting slower aging in the brain.

Sirtuins have received much celebrity recently, based on the therapeutic potential of sirtuin activators. The appeal of sirtuins as antiaging drug targets was elevated significantly by two related developments. First, studies carried out in yeast led to the proposal that Sir2 acts as a key downstream mediator of life-span extension from dietary restriction (Guarente and Picard, 2005). Dietary restriction, a reduction in nutrient availability without malnutrition, is known to increase life span in multiple organisms and to delay the onset of a variety of age-associated diseases in mammals. Second, the small molecule resveratrol was identified as an in vitro activator of Sir2 and was reported to increase life span in yeast, worms, flies, and one short-lived species of fish (Baur and Sinclair, 2006). More recently, resveratrol has also been reported to protect mice against negative health consequences of a high-fat diet, an effect attributed by the authors to activation of SirT1 (Baur et al., 2006; Lagouge et al., 2006).

Unfortunately, what has often been lost in reviews of the sirtuin literature and reports in the popular media are the many complexities and inconsistencies in our understanding of sirtuin biology as it relates to aging. For example, in yeast, Sir2 overexpression increases replicative life span, defined as the number of daughter cells produced by a mother cell, but shortens chronological life span, which is a measure of the length of time a yeast cell can survive in a nondividing state (Fabrizio et al., 2005). More perplexing is the observation that, although Sir2 orthologs promote longevity in yeast (replicative), worms, and flies, the currently available data suggest that they do so via different molecular mechanisms in each of these organisms (Figure 1). Consensus on several key questions related to sirtuin biology in aging has been difficult to achieve, as well. For example, multiple labs have reported that sirtuins are not always required for life-span extension from dietary restriction in either yeast or worms (Kaeberlein and Powers, 2007); the initial reports of Sir2-dependent life-span extension from resveratrol in yeast, worms, and flies has proven difficult to replicate (Bass et al., 2007; Kaeberlein et al., 2005); and resveratrol has been reported by different labs to activate, inhibit, or have no effect on sirtuins in vivo.

The situation regarding sirtuin biology in mammals is particularly complex. In addition to SirT1, there are six other mammalian sirtuins of diverse function and subcellular localization (Haigis and Guarente, 2006). SirT1 itself has been reported to deacetylate a plethora of substrates, including histones, p53, Ku70, NF-κB, PGC-1α, FOXO1, and PPARγ (Haigis and Guarente, 2006). Although most of the SirT1 knockout mice are embryonic lethal, the animals that survive appear relatively normal. Interestingly, SirT1 knockout animals fail to show increased life span in response to dietary restriction, consistent with the hypothesis that the life-span extension from dietary restriction is mediated by activation of SirT1; however, as Li et al. point out, this experiment is difficult to interpret due to the shortened life span of the SirT1 knockouts on a normal diet. Similarly, in yeast, *SIR2* deletion mutants are short lived and fail to respond to dietary restriction; however,

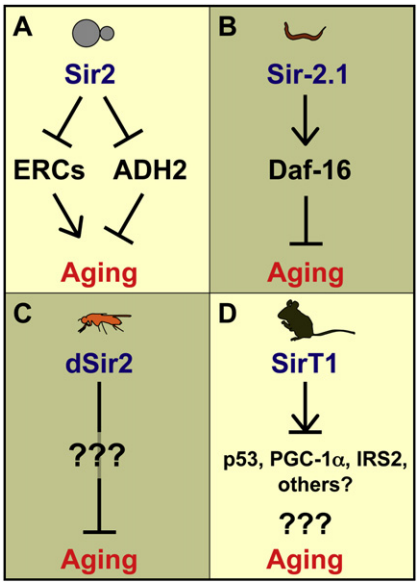

Figure 1. Different Mechanisms of Sir2 Longevity Control in Evolutionarily Divergent Organisms
(A) Sir2 slows yeast replicative aging by repressing the formation of extrachromosomal rDNA circles (ERCs), but accelerates chronological aging by reducing activity of the alcohol dehydrogenase encoded by *ADH2*.
(B) Sir-2.1 promotes longevity in *C. elegans* by regulating the FOXO-family transcription factor Daf-16.
(C and D) The molecular mechanism(s) by which dSir2 promotes longevity in flies remains unknown (C), and the extent to which SirT1 influences aging in mammals has yet to be determined (D).

when the life-span defect of *SIR2* deletion is suppressed by deletion of a second gene, *FOB1*, mother cells respond robustly to dietary restriction and live substantially longer than wild-type cells (Kaeberlein et al., 2004).

What makes the study by Li et al. particularly interesting is the observation that SirT1 inhibition causes some phenotypes more consistent with a slower rate of aging. For example, they show that SirT1 inhibition leads to increased IRS-2 acetylation, decreased IGF-1 signaling, and decreased Ras/ERK signaling. Decreased Ras signaling increases life span in yeast, and reduced insulin/IGF-1-like signaling is associated with increased life span in worms, flies, and mice. Supporting the idea that inhibition of SirT1 may slow aspects of aging in mice, Li et al. proceed to show enhanced resistance to oxidative stress in neuronal cells after SirT1 knockdown and reduced oxidation of proteins and lipids in brains of SirT1 knockout animals. Taken together, these data may indicate that inhibition of SirT1 can be neuroprotective in aging animals and that some features of aging are slowed rather than accelerated in SirT1 knockout animals.

So what's the "take-home message" from all this? Is more SirT1 good, or is less SirT1 good? The answer, as is often the case in biology, is that there's no simple answer. Activating SirT1 is probably a good thing in some cells under some conditions and is probably a bad thing in other cells under other conditions. SirT1 activators may be good for diabetes but may cause cancer due to p53 inhibition, SirT1 inhibitors may protect against cancer but cause metabolic disease, and there is evidence supporting the idea that both activators and inhibitors of SirT1 can confer protection against neurodegeneration in different contexts. The one thing that seems clear is that sirtuin activators are unlikely to be a "magic bullet" for aging. A more realistic hope is that, as we continue to unravel the complexities of sirtuin biology, targeted activation or inhibition of SirT1—and perhaps other sirtuins as well—will prove therapeutically useful toward a subset of age-associated diseases. Such an achievement would be a huge step forward in the transition of aging-related science from the laboratory to the clinic, and we eagerly await the next chapter in the unfolding saga that is sirtuin biology.

REFERENCES

Bass, T.M., Weinkove, D., Houthoofd, K., Gems, D., and Partridge, L. (2007). Mech. Ageing Dev. *128*, 546–552.

Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., Allard, J.S., Lopez-Lluch, G., Lewis, K., et al. (2006). Nature *444*, 337–342.

Baur, J.A., and Sinclair, D.A. (2006). Nat. Rev. Drug Discov. *5*, 493–506.

Fabrizio, P., Gattazzo, C., Battistella, L., Wei, M., Cheng, C., McGrew, K., and Longo, V.D. (2005). Cell *123*, 655–667.

Guarente, L., and Picard, F. (2005). Cell *120*, 473–482.

Haigis, M.C., and Guarente, L.P. (2006). Genes Dev. *20*, 2913–2921.

Kaeberlein, M., Kirkland, K.T., Fields, S., and Kennedy, B.K. (2004). PLoS Biol. *2*, E296.

Kaeberlein, M., McDonagh, T., Heltweg, B., Hixon, J., Westman, E.A., Caldwell, S.D., Napper, A., Curtis, R., Distefano, P.S., Fields, S., et al. (2005). J. Biol. Chem. *280*, 17038–17045.

Kaeberlein, M., and Powers, R.W., 3rd. (2007). Ageing Res. Rev. *6*, 128–140.

Lagouge, M., Argmann, C., Gerhart-Hines, Z., Meziane, H., Lerin, C., Daussin, F., Messadeq, N., Milne, J., Lambert, P., Elliott, P., et al. (2006). Cell *127*, 1109–1122.

Li, Y., Xu, W., Wei, M., Fabrizio, P., Parrella, E., and Longo, V.D. (2008). Cell Metab. *8*, this issue, 38–48.

Longo, V.D., and Kennedy, B.K. (2006). Cell *126*, 257–268.

Diabetes Risk Begins In Utero

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Both intrauterine and postnatal environments contribute to diabetes risk. A recent paper highlights epigenetic mechanisms underlying β cell dysfunction associated with intrauterine growth retardation, including repressive histone modification and DNA methylation during postnatal life. Thus, intrauterine stress can initiate a disturbing epigenetic cascade of progressive transcriptional repression linked to β cell failure.

The prevalence of childhood obesity and type 2 diabetes (DM) has increased dramatically in the past 50 years. While overnutrition and a sedentary lifestyle clearly contribute to these findings, the intrauterine and early postnatal environment are also key contributors to obesity and DM risk. A recent paper (Park et al., 2008) highlights epigenetic mechanisms linking intrauterine growth retardation to β cell dysfunction and diabetes risk.

The association between low birth weight and adult disease was first reported by David Barker (Barker et al., 1989). Barker accessed the records of 15,000 men and women born before 1930 whose medical history was meticulously documented by nurses in Hertfordshire, England. Using this information, he made a landmark observation: Birth weight is inversely correlated with the risk