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 longevity 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 have 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,
Diabetes Risk Begins In Utero

Melissa Woo1 and Mary-Elizabeth Patti1,*

1Research Division, Joslin Diabetes Center, 1 Joslin Place, Boston, MA 02215, USA
*Correspondence: mary.elizabeth.patti@joslin.harvard.edu
DOI 10.1016/j.cmet.2008.06.007

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...