Sirtuin 6 Builds a Wall Against Inflammation, Trumping Diabetes

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In 2014, more than two-thirds of U.S. adults were overweight or obese (1). These numbers have more than doubled over the past 50 years; ominously, obesity increasingly afflicts younger individuals, including children (2). Numerous deleterious health consequences are associated with obesity, including hypertension, dyslipidemia, type 2 diabetes, heart disease, and cancer (3,4). The costs associated with obesity in the U.S. are estimated to top $500 billion/year over the next two decades (5,6). Substantial literature has documented key roles for adipose tissue macrophages and hepatic Kupffer cells in driving chronic systemic inflammation and insulin resistance and their downstream sequelae in obesity (7).

The sirtuins (SIRT1–7) are NAD^+-dependent lysine deacetylases/deacylases critical for maintaining cellular and organismal homeostasis. A large body of work has demonstrated roles of sirtuins in regulating inflammatory responses and signaling through the insulin/IGF-1, mTOR, and AMPK pathways, all of which help mediate the adverse health consequences of obesity (8). SIRT6 is a chromatin-associated sirtuin implicated in metabolism, inflammation, stress responses, and genomic stability. Whole-body *Sirt6* knockouts (KOs) die by a month of age from a complex hypoglycemic degenerative phenotype. Conversely, transgenic male mice overexpressing SIRT6 show extended longevity, with preserved glucose tolerance, attenuated adipose inflammation, and reduced macrophage activation and accumulation in adipose tissue (9). *Sirt6* transgenics fed a high-fat diet (HFD) show diminished white adipose tissue accumulation, lower triglyceride and LDL cholesterol levels, and improved glucose tolerance. Molecularly, SIRT6 deacetylates histone H3 and pyruvate kinase muscle isozyme M2 (PKM2), among other targets (10,11).

In this issue of *Diabetes*, Lee et al. (12) elucidate a novel mechanism whereby SIRT6 suppresses insulin resistance and inflammation occurring in response to HFD by modulating macrophage inflammatory signaling (Fig. 1). They show that SIRT6 levels are reduced in macrophages from HFD-fed mice and in proinflammatory M1 macrophages. To further explore a role for SIRT6 in this cell type, they generated myeloid-specific *Sirt6* KOs (mS6KOs). Though unremarkable under standard feeding conditions, these animals show an aggravated metabolic phenotype during HFD: increased weight gain, elevated fasting glucose and insulin levels, and fatty liver, along with diminished insulin-induced tissue phospho-AKT levels. mS6KOs exhibit increased M1 macrophage infiltration in liver and fat, with a concomitant reduction of M2 type macrophages associated with tissue repair and attenuated inflammation. This effect appeared to be cell autonomous. Mechanistically, the authors link these effects to regulation of inflammatory signaling by SIRT6—specifically, of its known targets nuclear factor-κB (NF-κB), STAT3, and p38 mitogen-activated protein kinase. Genetic suppression of NF-κB signaling, or pharmacological STAT3 inhibition, suppressed the increased inflammation present in cultured SIRT6-deficient macrophages to control levels. The authors further implicate the SIRT6 target PKM2 as a STAT3 regulator involved in regulation of macrophage inflammation.

The study by Lee et al. (12) contributes to the literature by documenting the importance of SIRT6 in diverse cell types in maintaining metabolic homeostasis during HFD (Fig. 1). SIRT6 negatively regulates hepatic gluconeogenesis, represses glycolytic gene expression, and attenuates lipogenesis by inhibiting the SREBPs, transcription factors involved in lipogenesis and cholesterol biogenesis (11). In a genetic obesity model, SIRT6 reduces hepatic and serum cholesterol levels, whereas hepatocyte SIRT6 deletion results in fatty liver (11). SIRT6 modulates PGC1-α activity, suppressing hepatic glucose production (11). Adipose-specific SIRT6 deficiency resulted in increased FOXO1 acetylation, decreased lipolysis, and worsened obesity in response to HFD. HFD-induced insulin resistance, increased adipose tissue inflammation, and fatty liver were observed in these mice (13), consistent with the phenotypes of mS6KOs. *Sirt6* KO specifically in pancreatic β-cells results in exacerbated glucose

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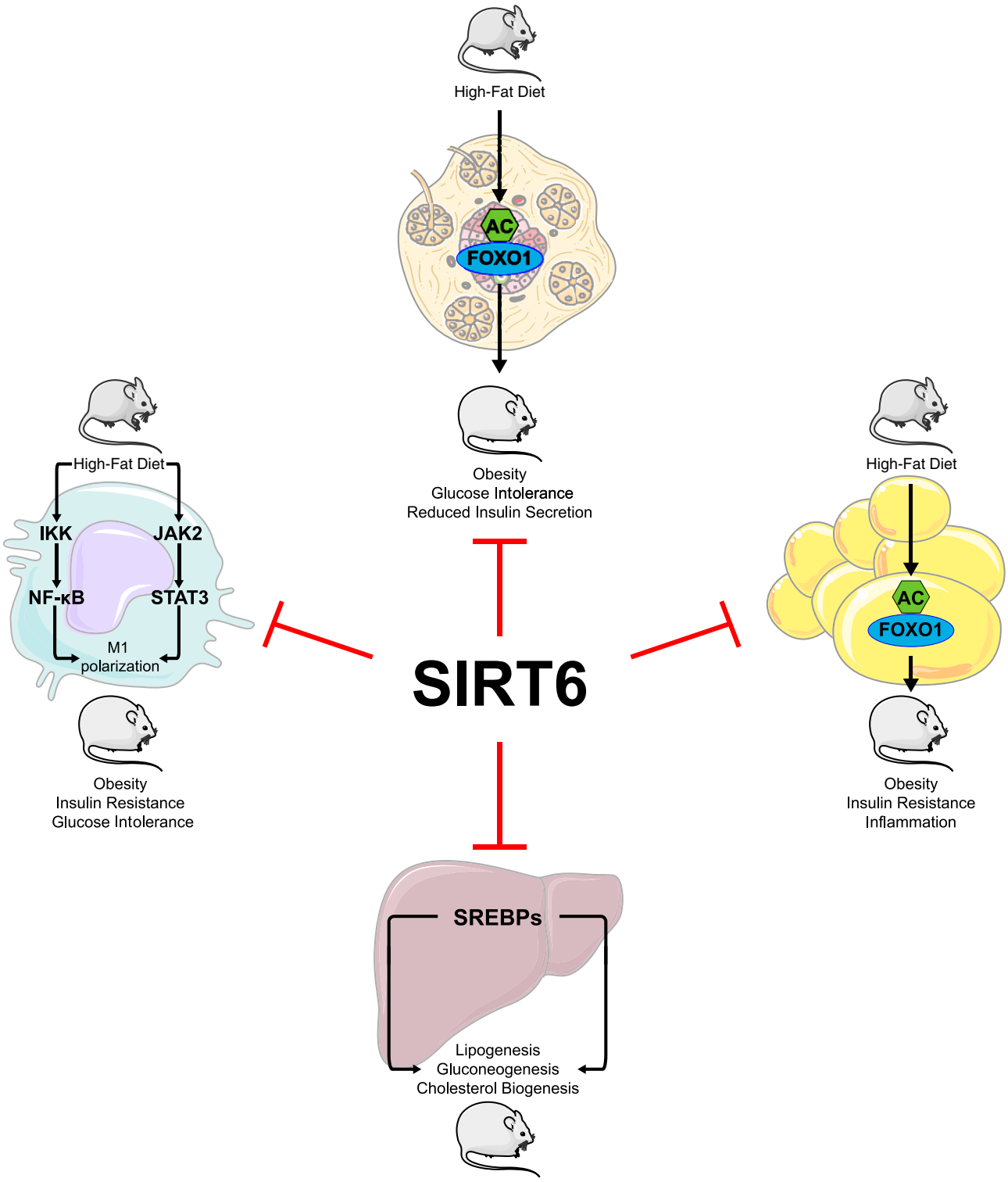

Figure 1—SIRT6 in macrophages inhibits inflammation via attenuation of NF-κB and JAK2/STAT3 signaling. SIRT6 in pancreatic β-cells, adipose tissue, and the liver inhibit glucose intolerance, inflammation, insulin resistance, and cholesterol biogenesis, among other negative impacts of HFD. Some graphics in this figure were obtained and modified from Servier Medical Art from Servier (www.servier.com/Powerpoint-image-bank).

intolerance and reduced glucose-stimulated insulin secretion during HFD (14). SIRT6-dependent FOXO1 deacetylation attenuates FOXO1-mediated transcriptional repression of critical glucose-sensing genes (15).

Might these functions of SIRT6 be relevant outside the context of a pathogenic diet? SIRT6 levels decline in dermal fibroblasts isolated from older donors (16). Likewise, NAD^+ levels decrease during HFD and in aged mouse tissues (17).

During natural aging, mice and humans show progressively decreased insulin sensitivity and increased sterile inflammation (18). It is interesting to speculate that impaired SIRT6 activity, in macrophages and other cells, may contribute to these changes. Perhaps pharmacological enhancement of SIRT6 activity, via lipid-based activators (8) or NAD^+ precursors (19), might help mitigate the effects of an unhealthy diet or even metabolic dysregulation associated with natural aging. However, caution is in order, since pharmacological inhibition of SIRT6 was recently shown to confer therapeutic benefit during HFD (20).

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