SirT1: A Guardian at the Gates of Adipose Tissue Inflammation

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Chronic, low-grade inflammation in adipose tissue is a characteristic of obesity that is intrinsically connected with fat expansion. The induction and maintenance of adipose tissue inflammation limits the ability of adipocytes to properly store nutrients and is strongly associated with systemic and adipocyte insulin resistance. The identification of inflammation as a link between obesity and type 2 diabetes has led to an explosion in research addressing how inflammatory cells (e.g., adipose tissue macrophages [ATMs] and T lymphocytes) and proinflammatory signaling networks interact with nutrient excess. This research has identified critical pathways that accelerate (e.g., nuclear factor-κB [NF-κB] and c-Jun *N*-terminal kinase [JNK] [1]) as well as those that suppress inflammation (e.g., the n-3 fatty acid receptor GPR120 [2]). Modulation of these signals may hold the key to unlocking future treatments for diabetes and metabolic syndrome.

The advances in the field of obesity-induced inflammation have shed new light on the dual ability of components of the innate immune system to control inflammation and nutrient metabolism (e.g., Toll-like receptors and the inflammasome). In line with this, Gillum et al. (3) present evidence that sirtuin 1 (SirT1) can function as a suppressor of adipose tissue inflammation. Their data lend further support to the concept that SirT1 sits at the nexus between energy homeostasis and inflammation.

The sirtuins are a family of deacetylases that regulate nutrient use via their ability to modify gene expression and target histones, metabolic transcription factors, and coregulators (e.g., peroxisome proliferator–activated receptor γ [PPARγ] [4]). Their ability to promote longevity overlaps with their importance in maintaining glucose homeostasis and insulin sensitivity. Activators of SirT1 improve insulin sensitivity in liver, muscle, and adipose tissue (5). In addition, SirT1 can repress inflammatory gene expression in both macrophages and adipocytes via suppression of JNK and NF-κB signaling (6,7). The dominant role of macrophage SirT1 in metabolism is inferred from the observation that the macrophage-specific deletion of SirT1 increased obesity-induced inflammation in the liver and fat with concomitant worsening of insulin resistance (8).

Gillum et al. set out to clarify the differential effects of SirT1 in macrophages and adipocytes in vivo by attenuating SirT1 expression with antisense oligonucleotides (ASOs). SirT1 expression in fat from lean mice and rats was decreased to levels that mimic the suppression seen with high-fat diet–induced obesity. Although some ASOs led to anorexia and weight loss, an increase in inflammatory cytokine expression was seen in fat and plasma with decreased SirT1. In adipose tissue, SirT1 knockdown triggered an increase in ATMs, which were biased toward an M1 classical macrophage activation gene expression profile with elevated expression of *Itgax* (CD11c) and *Tnfa*. Conversely, overexpression of SirT1 in transgenic animals led to a protection from obesity-induced inflammation. Importantly, human samples demonstrate an inverse correlation between SirT1 expression in fat and BMI and ATM content.

The findings by Gillum et al. strengthen the concept that the balance between proinflammatory and anti-inflammatory signals is important to adipose tissue function. Additionally, this study is unique in its application of ASO techniques to modify SirT1 activity, permitting the examination of several rodent models. However, although the adipose tissue inflammation induced by SirT1 attenuation is clear, it is unclear if such changes disrupt glucose or fatty acid metabolism in the ASO-treated lean mice beyond the anorexia observed.

These studies support a model in which SirT1 functions as a gatekeeper for the vicious cycle of inflammatory communication between adipocytes and ATMs (Fig. 1). An interesting aspect of the study is that the authors showed that macrophage-deficient mice had a similar induction of inflammation with treatment of the ASO. This implies that the ability of SirT1 to suppress inflammation in nonmacrophage cells in fat may be as or more important than its influence on ATM phenotypes. Although this likely involves blockade of SirT1 activity in adipocytes, this study does not exclude the possibility that SirT1 manipulation alters the function of adipose tissue T cells. $CD4^+$ and $CD8^+$ T cells in fat communicate with both ATMs and adipocytes and are significant contributors to the inflammatory response to obesity (9,10). There is ample evidence that SirT1 regulates lymphocyte function. Global Sirt1 deficiency results in an autoimmune phenotype caused by increased T-cell activation and a breakdown of self-tolerance (11). In contrast, targeted deletion of SirT1 in regulatory T cells promotes their ability to suppress immune responses (12).

The mechanisms that drive the increase in ATMs with SirT1 knockdown in the lean mice are unresolved in this study. The complement factor 3 was identified as a potential contributor. Besides chemokines, physiological stimuli such as lipolysis and fasting are sufficient to trigger macrophage recruitment to fat (13), and it is possible that metabolic cues lead to the increase in ATMs. Because SirT1 knockdown in adipocytes decreases lipolysis (4), mechanisms related to decreased insulin signaling and activation of JNK in SirT1-deficient adipocytes may modify ATM phenotypes (6). Another possible mechanism is that

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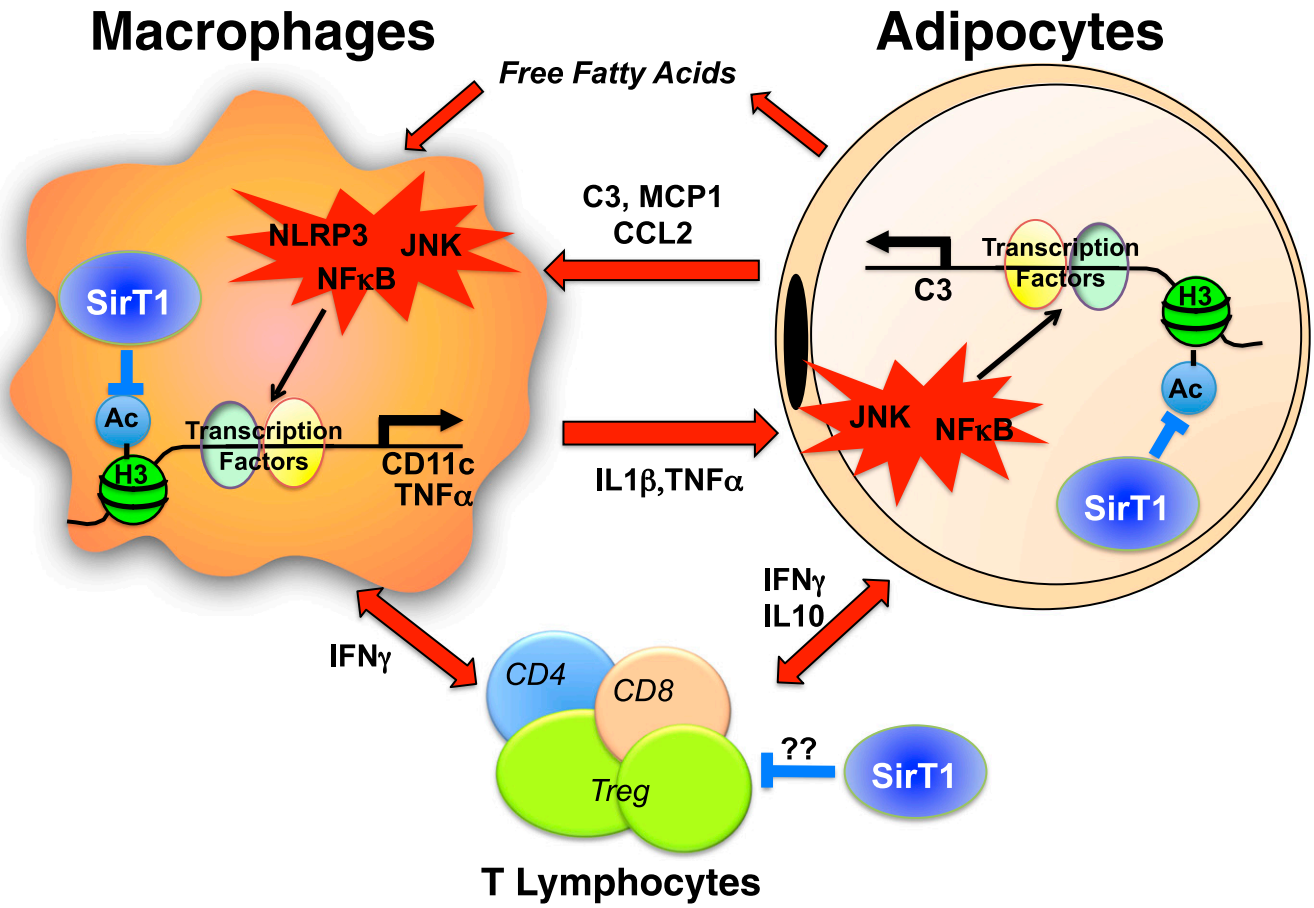

FIG. 1. The vicious cycle of adipose tissue inflammation. During obesity, nutrient excess and microenvironmental alterations lead to free fatty acids and cytokine release that recruits and activates inflammatory macrophages. ATM activation leads to local proinflammatory cytokine production triggered by innate immune sensors (e.g., JNK and the inflammasome). Cytokines talk back to adipocytes and contribute to further adipocyte dysfunction that amplifies inflammatory signals through a feed-forward loop. SirT1 suppresses the proinflammatory gene expression by deacetylating histones in adipocytes and macrophages and disrupting adipocyte-macrophage communication. T cells in fat can influence both ATMs and adipocytes and may be another target for SirT1 action. C3, complement factor 3; Tregs, regulatory T cells.

the knockdown of SirT1 expression triggered macrophage proliferation in fat, a newly appreciated mechanism in certain types of inflammation (14).

There are seven members of the mammalian sirtuin family of proteins (SirT1–7), and SirT1 is not the only one implicated in the regulation of inflammation. Both SirT2 and SirT3 are capable of inhibiting NF-κB–mediated inflammation via their deacetylase activity (15,16). Relevant to obesity, SirT3 has been shown to inhibit the inflammatory signals induced by free fatty acids that lead to chemokine production (16). In addition, caloric restriction can induce the expression of both SirT1 and SirT2 in peripheral monocytes, the circulating macrophage precursor (17). Overall, there may be broad and overlapping function of the sirtuins as negative regulators of adipose tissue inflammation that have yet to be revealed.

These findings further support the therapeutic potential of SirT1 activators for the obesity-induced metabolic diseases. In several rodent models of type 2 diabetes, SirT1 activators (e.g., resveratrol) and moderate SirT1 overexpression can ameliorate insulin resistance (18,19). The observation that SirT1 is decreased concomitantly with obesity raises questions regarding the approach to take with pharmacologic activation of SirT1. The induction of obesity-induced inflammatory changes in fat can be seen with mild obesity, therefore early treatment strategies may be of most benefit to block inflammation. Since obesity-associated inflammation can be seen in children as young as 3 years old (20), the therapeutic opportunity and challenge may lie in ways to promote SirT1 function in early disease states such as prediabetes. Overall, these findings shed light on another regulator of the "tone" of adipose tissue inflammation that opens the door to new treatment possibilities.

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No potential conflicts of interest relevant to this article were reported.

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