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# STAT4: An Initiator of Meta-Inflammation in Adipose Tissue?

Nelson H. Knudsen and Chih-Hao Lee

**M**etabolic regulation and immune signaling are closely linked, as evidenced by both the physical proximity between metabolic cells (e.g., adipocytes and hepatocytes) and resident macrophages as well as the progression of inflammation in metabolic syndrome. Contrasting the reactions to pathogen infections, meta-inflammation describes a novel type of low-grade, unresolvable immune response that is in the causal pathway to metabolic dysregulation (1). Although how meta-inflammation is initiated remains unclear, the T-helper cell type 1 (Th1)/Th2 (or M1/M2) paradigm provides a simplified view of how immune cells are involved in readjusting metabolic set points in response to nutrient intake (2). It appears that Th1 cytokines (e.g., interleukin [IL]-12 and interferon- $\gamma$  [IFN $\gamma$ ]) or Th1 polarized immune cells promote insulin resistance, whereas Th2 signaling (e.g., IL-4 and IL-13) sustains metabolic homeostasis (3). In mouse genetic models, for example, tipping the Th1/Th2 balance toward one specific spectrum leads to the expected outcome (4). As such, immunometabolism has become an attractive target to treat metabolic diseases.

Members of the signal transducer and activator of the transcription (STAT) family are transcription factors that mediate the signaling events of many cytokines in immune and nonimmune cells (5–7). The seven mammalian STAT proteins each contain a DNA-binding domain, a transactivation domain, and an Src homology 2 (SH2) domain; the latter is required for dimerization (5). When cytokines are bound to cell surface receptors, the associated Janus kinases (JAKs) are activated, leading to tyrosine phosphorylation of the given STAT proteins (5). Phosphorylated STATs form dimers, translocate to the nucleus, and bind specific response elements to activate transcription of target genes (6). Previous work has provided a good understanding of the function of STAT proteins in inflammation (7). More recently, alternative roles have been described for STATs in direct regulation of metabolic processes in a variety of tissues (Fig. 1). For example, activation of STAT1 by IFN $\gamma$  facilitates M1 macrophage polarization in adipose tissue, an underlying mechanism of insulin resistance (4,8). Not surprisingly, due to its critical role in IFN-induced responses, STAT1 also contributes to autoimmune  $\beta$ -cell death in the development of type 1

diabetes (9). In contrast, the IL-4/IL-13-STAT6 signaling pathway is required to maintain alternative macrophage polarization in healthy white adipose tissue (3). STAT6-deficient mice are more susceptible to developing insulin resistance and glucose intolerance when challenged with a high-fat diet despite less weight gain (10). In hepatocytes, IL-13 has been shown to suppress glucose production through a noncanonical, STAT3-dependent pathway (11). The emerging function of STAT proteins in direct metabolic regulation further underscores the intricate relationship between immune and metabolic pathways and implicates their potential to serve as therapeutic targets.

In this issue, Dobrian et al. (12) implicate STAT4 in the development of white adipose tissue (WAT) inflammation and insulin resistance. STAT4 is primarily activated by IL-12 to promote cytotoxic responses and Th1 cell differentiation. Consequently, STAT4 gene deletion leads to a Th2-biased phenotype (7). Dobrian et al. show that STAT4-deficient mice have improved insulin sensitivity and glucose tolerance when challenged with a high-fat diet. As expected, STAT4<sup>-/-</sup> WAT shows less macrophage infiltration with an M2 polarization phenotype, an observation that is likely due to a reduction in IFN $\gamma$ -producing T cells. There is also an increase in CD3<sup>+</sup>CD25<sup>+</sup> T-regulatory cells and a decrease in CD8<sup>+</sup> T cells. CD4<sup>+</sup> cells are not affected. These results are consistent with a previous study that implicated CD8<sup>+</sup> T cells in macrophage recruitment, adipose tissue inflammation, and systemic insulin resistance (13).

Interestingly, STAT4 appears to play a specific role in CD8<sup>+</sup> T-cell migration into adipose tissue. Two lines of evidence support this notion. First, IL-12 induces the production of CXCL10 and CCL5—chemokines that attract T cells—in WAT explants in a STAT4-dependent manner. Conditioned media from STAT4-deficient WAT explants were less effective at recruiting both CD4<sup>+</sup> and CD8<sup>+</sup> T cells. In addition, CD8<sup>+</sup> T cells derived from STAT4<sup>-/-</sup> mice showed a significant reduction in their migratory activities, indicating an intrinsic defect in migration. Indeed, expression of CCR3 and CCR5, which could serve as CCL5 receptors, is downregulated in STAT4-deficient CD8<sup>+</sup> cells. To further evaluate this function of STAT4, Dobrian et al. reconstituted Rag1 mice, which lack T, NKT, and B cells, with splenocytes of STAT4<sup>-/-</sup> mice and wild-type controls. Mice receiving STAT4-deficient splenocytes are more insulin sensitive and exhibit reduced WAT CD8<sup>+</sup> T cells. However, the improvement is milder compared with that observed with whole-body STAT4 deficiency.

Results from this study suggest that STAT4 activation in CD8<sup>+</sup> T cells may be one of the initial cues triggering immune cell migration into adipose tissue. Anatomically, WAT CD8<sup>+</sup> T cells appear to be specifically affected by STAT4 deficiency. Dobrian et al. demonstrate STAT4 is expressed in adipocytes, indicating that adipose STAT4 is also involved in CD8<sup>+</sup> T-cell recruitment/activation. In line with this notion, STAT4<sup>-/-</sup> fat explants were nonresponsive

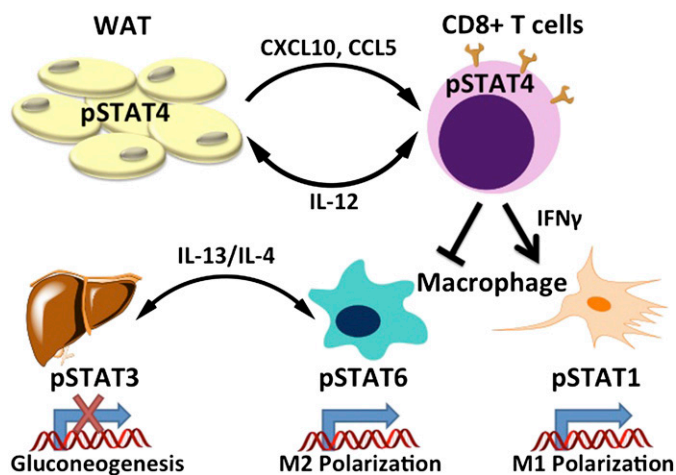
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See accompanying original article, p. 4109.



**FIG. 1. STAT proteins in regulation of metabolic tissue homeostasis.** The Th1/Th2 or M1/M2 paradigm describes how immune signaling modulates metabolic homeostasis, notably within adipose tissues. Phosphorylated STAT1 (pSTAT1) regulates M1 polarization of macrophages in response to Th1 cytokines, while pSTAT6 promotes M2 polarization. Additionally, Th2 cytokines activate pSTAT3 in the liver to suppress expression of gluconeogenic genes. Results from Dobrian et al. (12) suggest that the combined function of pSTAT4 in adipocytes and T cells leads to increased CD8<sup>+</sup> cell infiltration into WAT, where CD8<sup>+</sup> cell-derived IFN $\gamma$  mediates recruitment and activation of M1 macrophages, thereby contributing to metabolic dysfunction.

to IL-12-stimulated chemokine production, as described earlier. Furthermore, the splenocyte reconstitution experiment suggests that STAT4 in nonhematopoietic cells may also contribute to meta-inflammation. Approaches using conditional knockout models will be required to assess the tissue/cell type-specific function of STAT4. Another important question that deserves investigation is the source of IL-12 in WAT. M1 macrophages can produce IL-12. However, CD8<sup>+</sup> T-cell infiltration is thought to precede that of the M1 macrophage (13). Dobrian et al. (12) show reduced expression of IL-12 p35 and p40 subunits in STAT4<sup>-/-</sup> adipocytes. It will be interesting in future work to determine whether adipose STAT4 regulates feed-forward, IL-12 autocrine signaling in initiating meta-inflammation, and

whether pharmacologic inhibition of the IL-12/STAT4 pathway suppresses the WAT inflammatory response to improve metabolic homeostasis and insulin sensitivity.

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