

# PPAR $\delta$ -mediated macrophage activation: a matter of fat

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Chronic inflammation is increasingly recognized as an underlying factor in the development of several pathological disorders including obesity-associated metabolic disease, heart disease, atherosclerosis and rheumatoid arthritis. Macrophages, which are key sentinels of the innate immune system, play multiple roles in host defense as well as in whole-body homeostasis. Macrophage activation and infiltration into resident tissues dictates the local inflammatory response. In obese patients, increased infiltration of macrophages into the liver and adipose tissue is associated with the constellation of symptoms that define metabolic syndrome (Lumeng et al., 2007). Two recent reports in *Cell Metabolism* identify the nuclear hormone receptor PPAR $\delta$  (peroxisome proliferators-activated receptor delta) as a crucial signaling molecule controlling the phenotypic switch between classical proinflammatory (M1) and alternative anti-inflammatory (M2) macrophages (Kang et al., 2008; Odegaard et al., 2008). These studies demonstrate that PPAR $\delta$  encourages macrophages toward the alternative M2 phenotype, which improves fatty acid metabolism and insulin sensitivity, and suppresses systemic inflammation. The findings raise the intriguing possibility that small molecule agonists of PPAR $\delta$  may be effective therapeutic targets for the treatment of chronic inflammatory diseases.

Originating as myeloid cells in bone marrow, the macrophage lineage has the capability of producing circulating macrophages in the blood or specialized cells such as microglia, Kupffer cells, osteoclasts and adipose tissue macrophages (ATMs) within resident tissue. Macrophages quiescently survey the tissue milieu for signs of microbial infection or damage. In response to stimuli, macrophages undergo two distinct programs of activation deemed classical

(M1) and alternative (M2) (Gordon, 2003; Mantovani et al., 2004). Classically activated macrophages utilize glycolysis during their respiratory burst, releasing proinflammatory cytokines and reactive oxygen species. Alternatively activated macrophages rely on fatty acid oxidation for energy balance and are involved primarily in microbial monitoring and tissue repair (Gordon, 2003).

A major role for ATMs in the etiology of metabolic disease is emerging. Adipose tissue has an increased infiltration of macrophages (Weisberg et al., 2003; Xu et al., 2003), whereas lean animals have increased levels of alternatively activated macrophages and reduced inflammation (Mantovani et al., 2004). Additional evidence demonstrates that obesity represents a state of chronic low-grade inflammation that contributes to insulin resistance and type 2 diabetes. Lumeng et al. (2007) report that, upon high-fat feeding, murine macrophages migrate to adipose tissue where their accumulation and activation state correlates with body weight. High levels of classically activated macrophages with characteristic M1 surface markers localize to visceral fat. In obese mice, ATMs are prone to secrete high levels of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukin (IL)-6 and inducible nitric oxide synthase (iNOS), contributing to inflammation. However, lean mice display less macrophage infiltration and have higher percentages of alternatively activated M2 macrophages. Moreover, M2-polarized macrophages display high expression levels of the Th2 cytokine IL-6, a marker associated with insulin sensitivity in humans.

Although the Th2 cytokines IL-4 and IL-6, and signal transducer and activator of transcription 6 (STAT6), are known to mediate macrophage activation, recent evidence links the metabolic role of PPARs and

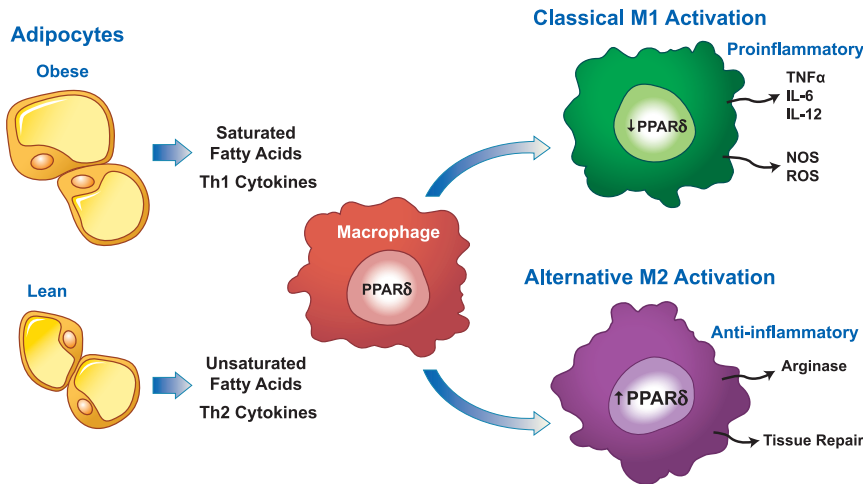
their coactivator proteins with macrophage phenotype switching. Work in macrophage cell lines (Vats et al., 2006) shows that Th2 cytokines induce the expression of PPAR $\gamma$  coactivator beta (PGC-1 $\beta$ ) in a STAT6-dependent manner. Similar to IL-4 expression, PGC-1 $\beta$  expression attenuates macrophage oxidative metabolism and stimulates the expression of proteins that are indicative of the less inflammatory alternative status. These findings support the notion that metabolic mediators of transcription may also serve as key regulatory elements in macrophage activation and the inflammatory response.

The recent papers by Kang et al. and Odegaard et al. provide a new twist to the story by showing a role for PPAR $\delta$  in macrophage class switching (Fig. 1) (Kang et al., 2008; Odegaard et al., 2008). In the macrophage, PPAR $\delta$  activation is known to suppress inflammation and induce genes that are involved in fatty acid catabolism (Barak et al., 2002; Lee et al., 2003). To explore the role of PPAR $\delta$  in macrophage activation, the two research groups used slightly different mouse models. Both lysozyme-Cre-specific deletion of PPAR $\delta$  in macrophages (Kang et al.) and an irradiated mouse reconstituted by PPAR $\delta$ <sup>-/-</sup> bone marrow (Odegaard et al.) showed that PPAR $\delta$  activation influences M2 macrophage activation (see fig. 1 in Kang et al. and fig. 1 in Odegaard et al.). However, differences emerge between the studies when Kang et al. demonstrate that the production of Th2 cytokines from local adipocytes and hepatocytes influences PPAR $\delta$  activation and, thus, the induction of the macrophage M2 phenotype (see fig. 2 in Kang et al.). The data of Odegaard et al. suggest that PPAR $\delta$  activation and macrophage switching is controlled through receptor binding of unsaturated fatty acid ligands (see fig. 3 in Odegaard et al.). Further investigation is needed to determine what endogenous factors influence PPAR $\delta$ -mediated macrophage activation.

Both papers demonstrate that the resulting PPAR $\delta$  activation leads to gene profiles that are characteristic of alternatively activated macrophages (see fig. 3 in Kang et al. and fig. 3 in Odegaard et al.). Elevated proinflammatory cytokine levels and markers of M1 macrophages are found in PPAR $\delta$ -deficient macrophages. Additionally, arginase 1, which is encoded by a signature gene that is induced during alternative

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**Fig. 1. Classical and alternative activation in macrophages.** Saturated fatty acids and Th1 cytokines from local adipocytes promote classical activation of macrophages. Classically activated macrophages release proinflammatory cytokines and reactive oxygen species. By contrast, lean adipocytes release unsaturated fatty acids and Th2 cytokines which activate PPAR $\delta$  signaling and alternative macrophage activation. Alternatively activated macrophages display high levels of arginase and are involved in tissue repair.

macrophage activation, is reduced markedly in both of the PPAR $\delta$  null mouse models. The metabolic consequences of PPAR $\delta$  deletion in macrophages, which are amplified by a high-fat diet, are glucose intolerance, insulin resistance and the development of fatty liver (see fig. 4 in Kang et al. and fig. 4 in Odegaard et al.). Kang et al. attribute this phenotype to increased lipolysis and decreased adiposity in the Cre-driven PPAR $\delta$  knockout mice (see fig. 5 in Kang et al.). Odegaard et al. believe that the phenotype is the result of impaired insulin signaling in the liver (see figs 4, 5 in Odegaard et al.). Both reports note that increased levels of saturated fatty acids in the high-fat fed mice contribute to classical activation and increased inflammatory cytokine expression. Conversely, macrophages in lean mice are exposed to higher amounts of unsaturated fatty acids, resulting in alternative activation. Interestingly, Odegaard et al. report higher adipos-

ity and larger adipocytes in their PPAR $\delta$  bone marrow transplantation model, which is in stark contrast to Kang et al. who observe the opposite scenario. A possible explanation for these phenotypic differences may be attributed to the slight differences in mouse models used in the studies.

Despite their differences, these reports highlight the dynamic roles that nuclear receptors and lipid profiles play in macrophage activation and metabolic disease. The ability of the macrophage activation state to affect insulin signaling and glucose homeostasis remains unknown. Kang et al. hint that cytokines and fatty acids from local adipocytes regulate macrophage activation and, thus, whole-body metabolism (see fig. 7 in Kang et al.). Odegaard et al. propose that abrogated PPAR $\delta$  signaling in adipose tissue macrophages and the homing of macrophages to the liver (Kupffer cells) contribute to the systemic insulin resistance that is seen in their animal model

(see fig. 7 in Odegaard et al.). A key question that emerges from these studies is how macrophage activation in the liver and adipose tissue may regulate parenchymal cell metabolism and systemic insulin sensitivity. It will be interesting to test the effectiveness of pharmacological agonists of PPAR $\delta$  in controlling macrophage activation during chronic inflammation and metabolic syndrome.

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