PPARδ-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 PPARδ (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 PPARδ 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 PPARδ 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 α (TNFα), 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 PPARγ coactivator beta (PGC-1β) in a STAT6-dependent manner. Similar to IL-4 expression, PGC-1β 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 PPARδ in macrophage class switching (Fig. 1) (Kang et al., 2008; Odegaard et al., 2008). In the macrophage, PPARδ 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 PPARδ in macrophage activation, the two research groups used slightly different mouse models. Both lysozyme-Cre-specific deletion of PPARδ in macrophages (Kang et al.) and an irradiated mouse reconstituted by PPARδ⁺/⁻ bone marrow (Odegaard et al.) showed that PPARδ 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 PPARδ 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 PPARδ 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 PPARδ-mediated macrophage activation.

Both papers demonstrate that the resulting PPARδ 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 PPARδ-deficient macrophages. Additionally, arginase 1, which is encoded by a signature gene that is induced during alternative

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macrophage activation, is reduced markedly in both of the PPARδ null mouse models. The metabolic consequences of PPARδ 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 PPARδ 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 adiposity and larger adipocytes in their PPARδ 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 PPARδ 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 PPARδ in controlling macrophage activation during chronic inflammation and metabolic syndrome.

**REFERENCES**


