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Research Update (Minireview)

# Eosinophils and Type 2 Cytokine Signaling in Macrophages Support the Biogenesis of Cold-induced Beige Fat

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Brown adipose generates heat via oxidation of fatty acids by a mitochondrial uncoupling protein 1 (UCP1)-dependent process. In addition, a subpopulation of cells within subcutaneous white adipose tissue, known as beige adipocytes, also plays a role in thermogenesis. The biogenesis of beige adipocytes is induced by thermogenic signals, such as chronic cold exposure. Recently, it has been reported that eosinophils, type 2 cytokines of IL-4/13, and alternatively activated macrophages control the thermogenic cycle of beige adipocytes. Alternatively, activated macrophages induce $UCP1^+$ beige adipocytes through secretion of catecholamines. These results define the role of type 2 immune responses in the regulation of energy homeostasis.

**Key Words:** Brown adipose tissue, Beige fat, Thermogenesis, Eosinophil, Type 2 cytokine

## INTRODUCTION

In an article published in Cell on June 5, 2014, Qiu *et al*. reported that cold-induced remodeling of subcutaneous white adipose tissue (scWAT) into thermogenic beige fat is dependent on eosinophils, type 2 cytokines, macrophages, and myeloid cell-derived catecholamines (1). In contrast to white adipocytes that store energy as triglycerides, brown adipose tissue (BAT) generates heat from the metabolism of fatty acid, a process that is dependent on mitochondrial uncoupling protein 1 (UCP1) (2). While it had long been accepted that BAT exists only in the interscapular region of newborns, recent studies have demonstrated that adult humans harbor a depot of brown adipocytes that are cold inducible and interspersed in the cervical, supraclavicular, and para-vertebral regions (3). These human brown adipocytes in adults share molecular and functional characteristics with beige adipocytes of rodents, which can appear within scWAT in response to chronic cold exposure or β3 adrenergic stimulation (4). When stimulated by such external cues, beige adipocytes express UCP1 at a similar level to classical brown adipocytes and exhibit UCP1-dependent thermogenic activity (5). UCP1 is localized in the inner membrane of mitochondria and activation of UCP1 in response to cold exposure results in heat generation by increasing oxidation of glucose and free fatty acids (2). As BAT is densely innervated, UCP1-mediated thermogenesis in this tissue is primarily regulated by the sympathetic nervous system (6). However, adipocytes in WAT are poorly innervated and alternative pathways

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involving starvation hormones, atrial and brain natriuretic peptides, and myokines have been suggested as factors influencing UCP1 expression in beige adipocytes in scWAT (6).

## The Role of Type 2 Immune Response in Beige Fat Biogenesis

To investigate the role of the type 2 immune response in the biogenesis of cold-induced beige fat, Qui *et al*. exposed wild-type (WT) and *Il4/13*$^{-/-}$ mice to a cold environment (5℃) for 48 h. They found that cold-induced remodeling of scWAT into beige fat was impaired in *Il4/13*$^{-/-}$ mice, as evidenced by a paucity of multilocular UCP1$^{+}$ adipocytes in the scWAT of these mice. Compared to WT mice, the scWAT of cold-exposed *Il4/13*$^{-/-}$ mice had significantly decreased expression of thermogenic genes and UCP1 protein, as well as decreased oxygen consumption. Mice with a depletion of IL-4 receptor α (IL-4Rα) and STAT6 also showed reduced browning of scWAT with defective UCP1 expression when housed at 5℃. Oxygen consumption also decreased in *Il4ra*$^{-/-}$ and *Stat6*$^{-/-}$ mice, and these mice were unable to maintain body temperature upon cold exposure. Collectively, these results indicate that type 2 immunity and the associated downstream signaling, specifically the IL-4/13-IL-4Rα-STAT6 pathway, are required for the biogenesis of functional beige fat (1).

Eosinophils are granulocytic leukocytes that are rare in healthy individuals, but are markedly increased during parasitic infection and allergic inflammation (7). Although eosinophils have been considered destructive inflammatory cells, the involvement of eosinophils in antibody responses in the gastrointestinal tract has been provided (8, 9). In addition, eosinophils in adipose tissue function in differentiation of alternatively activated macrophages and regulation of insulin sensitivity (10). Using 4get-ΔdblGATA mice, which have selective depletion of IL-4-competent eosinophils, Qui *et al*. found that eosinophils in the scWAT are required for cold-induced transformation of scWAT into beige fat. Furthermore, they suggest that eosinophil IL-4 production may promote cold-induced beige fat transformation in a manner dependent on alternative activation of macrophages (1). Macrophage responses are classified into two distinct activation program, termed classical and alternative. Classical activation occurs in response to products associated with bacterial infections and results in highly inflammatory macrophages. In contrast, alternative activation occurs in response to type 2 cytokines, such as IL-4 and -13 (11). Mice lacking CCR2 (the chemokine receptor required for the recruitment of macrophages) or IL-4Rα in myeloid cells were unable to transform their scWAT into beige fat upon cold exposure. In addition, compared to macrophages in mice kept in a thermoneutral environment, macrophages in the scWAT of cold-exposed mice had higher expression of the alternative macrophage activation markers of arginase 1. Qui *et al*. also showed that *Il4ra*$^{f/f}$ *Lyz2*$^{Cre}$ mice, which lack *Il4ra* in myeloid cells, had fewer UCP1$^{+}$ beige adipocytes and lower rates of oxygen consumption at 5℃ (1).

When mammals are exposed to a cold environment for a prolonged period of time, sympathetic nerves are stimulated and the subsequent release of norepinephrine induces the development of beige fat (12). Based on their previous observation on the production of catecholamine by alternatively activated macrophages (13), Qui *et al*. investigated the norepinephrine synthetic effects of macrophages in cold-induced browning of scWAT. Their study revealed a dramatic increase of tyrosine hydroxylase, which is the rate-limiting enzyme for norepinephrine synthesis in scWAT upon cold exposure, although scWAT is poorly innervated by sympathetic nerves. The expression of tyrosine hydroxylase was observed in the scWAT macrophages in an IL-4/13- and IL-4Rα-dependent manner. To address the contribution of myeloid cell-derived catecholamines conclusively, Qui *et al.* produced mice selectively deficient for tyrosine hydroxylase in myeloid cells (*Th*$^{f/f}$*Lyz2*$^{Cre}$). The production of norepinephrine, expression of UCP1, and cold-induced browning were reduced in the scWAT of *Th*$^{f/f}$*Lyz2*$^{Cre}$ mice housed at 5℃. These data demonstrate that myeloid cell-derived catecholamines regulate metabolic remodeling of scWAT into thermogenic beige fat (1).

To address whether pharmacologic activation of type 2 cytokines affects the cold-induced remodeling of scWAT, Qui

*et al*. administered recombinant IL-4 to WT mice housed at 30℃, a temperature at which mice lack the thermal drive for beige fat biogenesis. IL-4 treatment increased expression of UCP1, arginase 1, and tyrosine hydroxylase in the scWAT and promoted energy expenditure during thermal stress. Administration of IL-4 also improved the metabolic phenotype of mice with diet-induced obesity, as evidenced by decreased body and fat mass. Insulin responsiveness accompanied by decreased levels of triglycerides and cholesterol was also observed in IL-4-treated obese mice (1).

## CLOSING REMARKS

This study shows that the immunologic circuit consisting of eosinophils, type 2 cytokines, and alternatively activated macrophages regulates the development of cold-induced beige fat. The local production of catecholamines by alternatively activated macrophages rather than sympathetic nerves induces the biogenesis of beige fat. The findings presented by Qui *et al*. will support therapeutic application of beige fat biogenesis in treating metabolic diseases associated with obesity.

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