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Adipose tissue-resident macrophages (M2-like) regulates proliferation of white and beige progenitors

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Previous reports suggested that adipose tissue macrophages are involved in maintaining insulin sensitivity in adipocytes along with improvement in metabolic genes. Nonetheless, it is largely unknown how depletion of M2-like macrophages regulates insulin sensitivity and adipocyte progenitor (AP) proliferation. To understand the role of M2-like macrophages in white adipose tissue (WAT), we generated CD206DTR mice based on transgenic expression of diphtheria toxin receptor under the control of the CD206(+) promoter to specifically deplete CD206 M2-like macrophages. Partial depletion of CD206 M2-like macrophages resulted in the generation of smaller adipocytes, upregulated expression of metabolically favorable genes and enhanced insulin sensitivity in both chow and high-fat diet-fed CD206-reduced mice. In vivo and in vitro studies revealed that Tgf<1, abundantly expressed in CD206 M2-like macrophages, regulate AP differentiation and proliferation. Flow cytometry analysis revealed that the number of APs was increased and cyclin gene expression levels in the AP fraction were up-regulated. To validate this hypothesis, we generated genetically engineered mice in which CD206 specific Tgfβ1 was knocked out after tamoxifen treatment. Increased number of APs and smaller adipocytes were observed in the CD206 specific Tgfβ1 knockout mice, suggesting that CD206 cell-specific deletion of Tgfβ1 resulted in the enhanced proliferation of AP. Previous studies had shown that type 2 cytokines and M2 macrophages induce cold-induced browning in inguinal WAT (ingWAT) by producing catecholamines. Exactly how the conditional and partial depletion of CD206 M2-like macrophages regulates the cold-induced browning of ingWAT, however, remains unknown. We also examined the role of CD206 M2-like macrophages in the cold-induced browning of WAT and found that partial depletion of CD206 M2-like macrophages caused an increase in the number of beige progenitors and also enhanced their proliferation in ingWAT in response to cold. Thus, we concluded that CD206 M2-like macrophages inhibit the proliferation of white and beige progenitors.

Keywords: Adipocyte progenitors, adipose tissue macrophages, beige adipocyte, insulin sensitivity.