Physiological Role of Immune Cells in Type 2 Diabetes

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ABSTRACT

Previous reports show that immune cells or adipose tissue-resident macrophages (ATMs) are involved in maintaining insulin sensitivity in adipocytes along with improvement in metabolic genes. ATMs are categorized into two subtypes, the M1-like and M2-like macrophages. M2-like macrophages are reported to play anti-inflammatory roles and to be involved in clearing and removal of dying/dead adipocytes and recruiting adipocyte progenitors (APs). However, the precise role of M2-like macrophages in the regulation of adipocyte progenitors is not fully known. Recently, we generated genetically engineered transgenic mice in which CD206+ M2-like macrophages can be conditionally depleted. Unexpectedly, we found that the depletion of CD206+ M2-like macrophages resulted in enhanced generation of smaller adipocytes, improved insulin sensitivity, and proliferation of APs. We further clarified that the CD206+ M2-like macrophages directly interact with the APs to regulate their growth/differentiation and adipogenesis, thereby controlling adiposity and systemic insulin sensitivity. I will discuss in detail how CD206+ M2-like macrophages involved in the regulation of progenitor`s proliferation in adipose tissue and muscle.

Keywords: Immune cells, pathophysiology of adipose tissue, Adipose tissue-resident macrophages, Adipose tissue niche, Adipocyte progenitors.

INTRODUCTION

Recently, the prevalence of obesity has been increasing, posing a burden on the health of the population worldwide (Heymsfield and Wadden). The increase in the prevalence of obesity has been attributed to an increasingly sedentary lifestyle and westernization of the diet. During progression of obesity, adipose tissue undergoes either adipocytes (hypertrophy) or hyperplasia(Odegaard and Chawla "Alternative Macrophage Activation and Metabolism"; Qiu et al.; Lee, Petkova and Granneman). We and other have previously demonstrated that the size of adipocytes is inversely related to the insulin sensitivity; namely, insulin resistance is associated with larger adipocytes, and insulin sensitivity with smaller adipocytes(Nawaz et al.; Okuno et al.). When the pool size of APs is sufficiently large, the adipose tissue undergoes hyperplasia through enhanced recruitment of APs that differentiate into small adipocytes in response to energy excess, thereby maintaining insulin sensitivity. When the pool size of APs is small, excess nutrients are taken up by the existing adipocytes, eventually resulting in an increase in the size of the cells, generation of reactive oxygen species, recruitment of macrophages, and induction of inflammation, thereby leading to insulin resistance. It would appear that whether adipocytes undergo hyperplasia or hypertrophy depends on the pool size of the APs. AT contains

several cell types, including APs, endothelial cells, fibroblasts, and immune cells, etc., that interact with each other to maintain tissue homeostasis(Lee, Petkova and Granneman; Jones and Wagers; Cinti). AT niches may regulate AP pools by expressing some adhesion molecules or other factors to maintain AT homeostasis and tissue repair(Morrison and Spradling; Scadden; Cinti). While ATMs are considered to be metabolically beneficial macrophages to preserve adipocyte health in a lean state. They are also reported to be involved in AT remodeling during progression of obesity(Wynn, Chawla and Pollard). ATMs are categorized into two subtypes, namely, (M1-like) proinflammatory macrophages, which cause AT hypertrophy and worsen insulin resistance, and (M2-like) anti-inflammatory macrophages, which improves insulin sensitivity(Lumeng, Bodzin and Saltiel; Fujisaka et al.; Odegaard and Chawla "Pleiotropic Actions of Insulin Resistance and Inflammation in Metabolic Homeostasis"). In addition, they play a role in adapting to excess energy states, because M2-like macrophage dysfunction caused by genetic disruption of the M2 gene results in metabolic disorders under high-fat diet conditions that are probably attributable to their anti-inflammatory functions(Satoh et al.). It has also been reported that M2-like macrophages are involved in the removal of dying adipocytes(Lee, Petkova and Granneman; Fischer-Posovszky et al.; Y. H. Lee, R. I. Thacker, et al.), recruitment of new progenitors(Y. H. Lee, A. P. Petkova, et al.; Y. H. Lee, R. I. Thacker, et al.) and promotion of white and beige adipocyte differentiation(Y. H. Lee, R. I. Thacker, et al.; M. W. Lee et al.; Qiu et al.), thus maintaining adipose tissue homeostasis and systemic insulin sensitivity. It is still unknown how the proliferation and differentiation of APs are regulated by M2-like macrophages within WAT, thus controlling the insulin sensitivity.

AIMS

To clarify the mechanism how $CD206^+$ M2-like macrophages in adipose tissue are involved in maintaining the insulin sensitivity.

METHODS

We generated transgenic mice to specifically ablate $CD206^+$ cells utilizing a conditional cell ablation system based on the transgenic expression of the human diphtheria toxin receptor under the control of CD206-positive promoter.

RESULTS

Previous reports show that M2-like ATMs are metabolically ‘good’ ATMs (Odegaard et al.), when compared with M1 pro-inflammatory macrophages, $CD206^+$ macrophages depletion might possibly deteriorate glucose metabolism despite enhanced APs proliferation. Then, we observed a decrease in the gluconeogenesis-related gene expression levels in the liver and increased mitochondrial gene expression in the skeletal muscle. We show that adipose tissue $CD206^+$ cells are primarily M2-like macrophages, and ablation of $CD206^+$ M2-like macrophages improves systemic insulin sensitivity, which was associated with an increased number of smaller adipocytes. Here, we show that M2-like macrophages in adipose tissue regulate systemic glucose homeostasis by inhibiting adipocyte progenitor proliferation via the CD206/TGFβ signaling pathway.

CONCLUSION

Our findings indicate that $CD206^+$ M2-like macrophages in adipose tissues create a microenvironment that inhibits growth and differentiation of adipocyte progenitors and, thereby, control adiposity and systemic insulin sensitivity. Inhibition of $CD206^+$ M2-like macrophages may be a new therapeutic target for maintaining systemic energy and glucose metabolism.

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