Commentary

TREM2-Positive Lipid-Associated Macrophages (LAMs) Control White Adipose Tissue Remodeling and Metabolic Adaptation in Obesity

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ABSTRACT

White adipose tissue (WAT) depots are populated with a large range of immune cells under both normal and obese conditions. During the progression of obesity, these immune cells increase in total abundance and in particular macrophage subpopulations change dramatically. However, origin, characteristics, and functions of adipose tissue macrophages in obesity are poorly understood. In a recent publication, Jaitin et al. develop an immune cell atlas of obese fat and identify a subclass of triggering receptor expressed on myeloid cells 2 (TREM2)-positive, so called lipid-associated macrophages (LAMs) which are critical determinants of adipose tissue homeostasis.

KEYWORDS: adipose tissue; macrophages; obesity; TREM2; immune cells; lipids

Obesity is a strong risk factor for the development of metabolic pathologies such as type 2 diabetes and its pandemic spread threatens human health. Immune cells existing in obese adipose tissue are implicated in the development of metabolic dysfunction with macrophages being the predominant immune cell population [1,2]. Earlier studies suggest a phenotypical switch of anti- to pro-inflammatory macrophages in adipose tissue during the progression of obesity [3,4] and there is accumulating evidence of multiple discrete adipose tissue macrophage (ATM) subpopulations adapting to environmental requirements, maintaining tissue homeostasis and protecting metabolic health [5,6]. However, regulation, origin, and distribution of these ATM subpopulations during the development of obesity are poorly characterized.

To address this open question, Jaitin et al. utilized cutting edge technologies to map adipose immune populations in WAT of obese mice and humans [7]. By means of massively parallel single-cell RNA-sequencing, the authors generated a mouse and human immune cell atlas, allowing the comparative analysis of various immune cell populations

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under obese conditions. Importantly, by time-resolved single immune cell characterization during the progression of diet-induced obesity in mice, the authors discovered a novel subset of macrophages, dubbed lipid associated macrophages (LAMs). Based on their transcriptome, these macrophages are uniquely equipped with the enzymatic machinery to recognize, scavenge and catabolize lipids. In particular, amongst others, they highly express fatty acids transporter *Cd36*, fatty acid binding proteins 4 and 5 (*Fabp4*, *Fabp5*), lipoprotein lipase (*Lpl*) and lysosomal acid lipase (*Lipa*), which facilitate the processing and degradation of lipids. Importantly, LAMs are localized to crown-like structures, suggesting that they specialized in the removal of hypertrophic, dying adipocytes. Moreover, Jaitin et al. discovered TREM2 as an essential driver of LAM generation. Noteworthy, they showed that loss of TREM2 aggravates WAT hypertrophy in response to high fat diet feeding, which is associated with worsened metabolic parameters including body fat content, plasma cholesterol and glucose tolerance. This indicates that TREM2-positive LAMs are important to dampen detrimental metabolic remodeling in obese WAT (Figure 1).

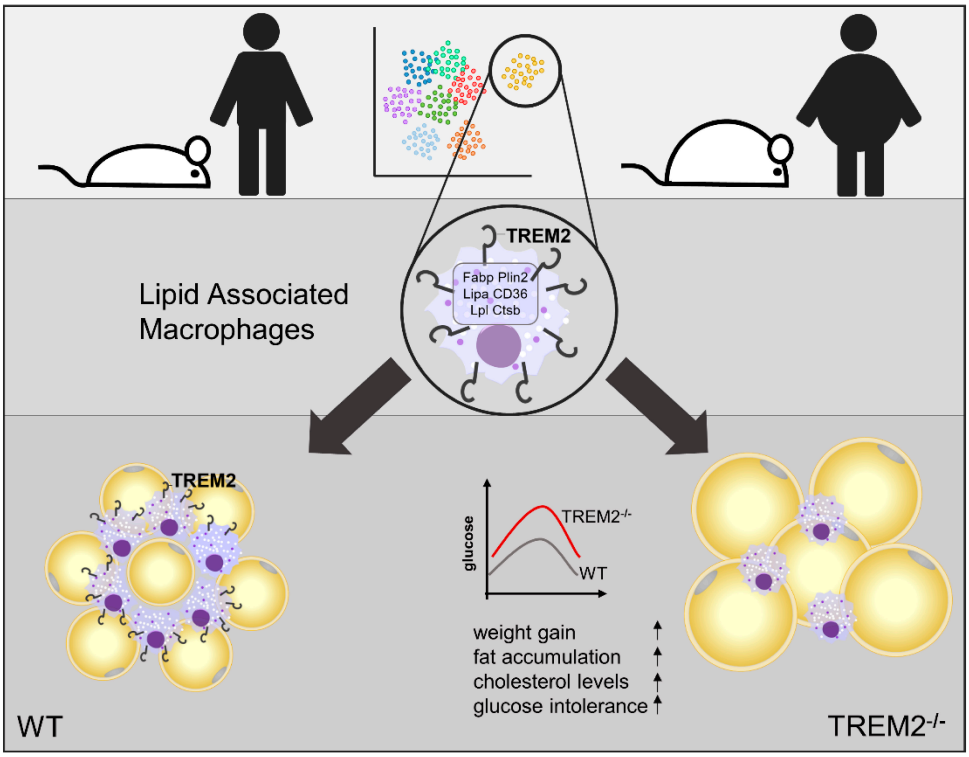

Figure 1. Performing massively parallel single-cell RNA-sequencing of lean and obese human and murine adipose tissues, Jaitin et al. create a map of adipose immune cells and identify a subpopulation of lipid-associated macrophages (LAMs), which arise during obesity. LAMs are equipped with a unique lipid catabolizing machinery and their generation is dependent on the lipid receptor TREM2. By mediating phagocytosis of dying adipocytes TREM2-positive LAMs control adipose tissue adaptation to obesity. In contrast, loss of TREM2 prevents LAM formation causing adipocyte hypertrophy, weight gain, and insulin resistance.

TREM2 is a transmembrane receptor of the immunoglobulin superfamily binding anionic ligands such as bacterial LPS, phospholipids, (apo)lipoproteins and cholesterol-containing myelin fragments [8–11]. Initially, TREM2 was identified in monocytes and macrophages where it has been shown to regulate inflammatory processes [12,13]. Later, variants of TREM2 were identified to be associated with the progression of Alzheimer disease (AD) [14]. Here, expression of TREM2 in microglia has been shown to boost their metabolism and function [9,15]. Transcriptomic analysis of microglia revealed a unique population of phagocytic so called disease associated microglia (DAM), which cluster around Aβ plaques and thus protect surrounding neuronal tissues. Interestingly, TREM2 has been implicated in DAM generation [16,17]. By discovering a crucial role of TREM2 also in LAM generation, Jaitin et al. highlight the outstanding function of TREM2, which might be generally implicated in recognition and removal of lipid-containing cell debris. Most likely, lipid sensing by TREM2 equips macrophages being in direct contact to either Aβ plaques or apoptotic adipocytes with a lipid catabolizing machinery, and thus controls tissue remodeling. This hypothesis is further strengthened by the discovery of TREM2-positive macrophages in atherosclerotic lesions [18] as well as in fibrotic liver [19]. Of note, the findings of Jaitin et al. are not limited to murine data. Single cell RNA sequencing in WAT from six obese vs. one lean humans yielded similar findings, further emphasizing their significance. In addition to previous studies analyzing ATM on single cell level [5], the elegant study by Jaitin et al. expands our knowledge on adipose immune cell functions during obesity. In brief, Jaitin et al. create a time resolved map of not only ATMs but also other immune cell populations in adipose tissues. Although the presence of a lipid catabolizing subpopulation of macrophages surrounding dying adipocytes has been described before [5,20], using TREM2-deficient mice and performing bone marrow transplantation experiments, Jaitin et al. underpin the importance of an immune cell intrinsic function of Trem2 and its downstream initiated lipid catabolizing program for the reorganization of adipose tissue. In accordance with recent work [6], their study reinforces the concept to discriminate between detrimental versus beneficial ATM populations and emphasizes the need to consider this fact when designing immune cell targeted therapies.

The work of Jaitin et al. raises new interesting issues: First, the exact pathways for a TREM2-dependent recognition of dying adipocytes as well as the intracellular signaling pathways in LAMs need to be elucidated. Furthermore, the TREM2 ligands present on hypertrophic and/or dying adipocytes need to be identified. Potential candidates include aminophospholipids of apoptotic cells as suggested by Shirotani et al. [21]. Next, it needs to be investigated if lipid recognition by TREM2 alone is crucial for function of LAMs or if the cellular machinery to take up and catabolize lipids is also important. Another question to be addressed would be the role of LAMs for other metabolic challenges beyond obesity,

such as postprandial conditions leading to overload of dietary lipids or catabolic challenges of prolonged fasting associated with high intracellular lipolysis and free fatty acid release. Moreover, it would be important to understand the role of LAMs in other adipose tissues including specialized WAT depots and brown adipose tissues [22]. Last but not least, a yet unresolved but clinically relevant question is whether LAMs and TREM2 can be targeted therapeutically in obesity. In this context, it is of note that TREM2 is subject to shedding by secretases. Accordingly, inhibition of these proteolytic enzymes might enhance TREM2 signaling [23], and thus maintain adipose tissue health in obesity. Moreover, small metabolites mimicking lipid ligands as well as agonistic TREM2 antibodies are potential therapeutic avenues targeting LAM activity for the treatment of obesity-related diseases. Future studies should aim to deepen mechanistic insights that may then lead to novel therapeutic options to prevent disease progression in different organs.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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