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Research paper

Adipose tissue macrophages and their polarization in health and obesity

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ABSTRACT

Adipose tissue is a special tissue environment due to its high lipid content. Adipose tissue macrophages (ATMs) help maintain adipose tissue homeostasis in steady state by clearing dead adipocytes. However, adipose tissue changes drastically during obesity, resulting in a state of chronic low grade inflammation and a shift in the adipose immune landscape. In this review we will discuss how these changes influence the polarization of ATMs.

1. Introduction

People gain weight when their energy intake exceeds the energy demand of their body. As a consequence, the excess energy is stored in the adipose tissue. However, adipose tissue is not just a neutral storage place for lipids, it is considered to be an endocrine organ that can secrete a wide range of hormones and adipokines that regulate systemic metabolism [1]. Adipose tissue is mostly composed of adipocytes, but it also contains resident immune cells that help maintain organ homeostasis. From these, adipose tissue macrophages (ATMs) are the most abundant leukocyte population, constituting around 5% of the adipose tissue in lean state, which increases dramatically in conditions of obesity both in humans and in mice (up to 50% of adipose tissue) [2]. Obesity is associated with a low grade inflammatory state, characterized by elevated serum levels of inflammatory mediators such as TNF and IL-1β, and the presence of circulating bacterial lipopolysaccharide (LPS), which induce inflammation in different metabolic tissues. In visceral fat, this is accompanied by a dramatic shift in the immune landscape with more pro-inflammatory immune cells inducing inflammatory responses. This shift is most apparent in ATMs, as these cells not only greatly expand in number, but also shift their phenotype from so-called alternatively activated 'M2' macrophages to classically activated 'M1' macrophages [3]. In lean conditions, ATMs express classical 'M2' genes such as *IL-10, Mrc2, Ym1/Chi3l3* and *Mgl1/2*, while in obese fat ATMs mainly express pro-inflammatory genes such as *IL-6* and *Nos2*, reminiscent of classical 'M1' macrophages [4]. In addition, both ATM populations can be distinguished based on the expression of surface markers, where in lean fat tissue the majority of ATMs express CD206, while in obese conditions M1-like macrophages accumulate and upregulate CD11c (Table 1). This distinction between both types of macrophages is also reflected in their location, as $CD206^+$ M2 macrophages mostly reside interstitially in between the adipocytes, while $CD11c^+$ M1 macrophages are mainly found in Crown Like Structures (CLS) [5]. According to the current hypothesis, this phenotypic switch of ATMs is believed to be crucial to promote the pro-inflammatory environment in obese adipose tissue, affecting insulin sensitivity in peripheral organs [6,7].

2. ATMs regulate adipose tissue homeostasis in steady lean state

Adipose tissue macrophages are the tissue resident macrophages of adipose tissue and they are important to help maintain tissue homeostasis in steady state. Their main function is to engulf dead adipocytes to help in the cellular turnover of these cells. In the lean state, ATMs occasionally form a CLS around a dying adipocyte, however, since adipocytes are much larger compared to ATMs, they are not able to engulf the entire adipocyte. To solve this, the ATMs form an extracellular acidic compartment around the dead adipocyte, by the release of their lysosomal enzymes through exocytosis, as shown in humans and in mice. As a result, the lysosomal enzymes liberate the free fatty acids (FFA), which are then taken up by the macrophages to be processed [8]. Interestingly, when adipocyte apoptosis is induced in mice, mostly alternatively activated $CD206^+$ M2 macrophages are recruited [9]. This indicates that adipocyte death alone is not enough to drive the switch to more inflammatory M1 macrophages suggesting that other factors, including live adipokine-secreting adipocytes are necessary to sustain the inflammation in adipose tissue. Moreover, the process of CLS formation and the clean removal of dead adipocytes is considered to be beneficial for tissue homeostasis, but in obese conditions this system is clearly out of balance.

Besides their role in the removal of dead adipocytes, ATMs also buffer part of the lipid pool present in the adipose tissue. When lipolysis

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Table 1
Markers for adipose tissue macrophages.

	ATMs	M1 ATMs	M2 ATMs
Mouse	$CD45^+$ $CD11b^+$ $F4/80^+$ *Optional:* $CD64^+$ Siglec F^- $Ly6G^-$ $Ly6C^-$	$CD11c^+$ *Optional:* $MHCII^+$ $iNOS^+$	$CD206^+$ *Optional:* $CD301^+$ Arginase 1^+
Human	$CD68^+$ $CD14^+$	$CD11c^+$	$CD163^+$ *Optional:* $CD204^+$ $CD206^+$

is induced due to weight loss or starvation, ATMs get recruited to the adipose tissue, adopt an anti-inflammatory phenotype and take up the released lipids [10]. Hence, when macrophages are depleted from the abdomen and lipolysis is induced in mice, FFA levels in the serum rise extensively. These findings demonstrate that local lipid fluxes regulate ATM recruitment to buffer local increases in lipid concentration [10]. In obese conditions, the macrophages in the CLS also contain multiple lipid droplets and resemble foam cells, both in human and murine adipose tissue, however, here the lipid buffering capacity is insufficient to cope with the nutrient overload [6,11]. M1 polarization is associated with the accumulation of lipid species in mouse ATMs, which coincides with the induction of gene-expression networks associated with lipid uptake, storage, and metabolism [12]. Interestingly, the lipid trafficking protein fatty acid transport protein 1 (FATP1) in mouse macrophages was shown to play a critical role in suppressing macrophage activation and adipocyte inflammation through modulation of glucose metabolism and oxidative stress, identifying FATP1 as a regulator of immunometabolism [13]. Further research on lipid buffering and macrophage polarization in the context of obesity would be important to fully understand the metabolic changes in adipose macrophages and its resulting consequences.

Recently, a lot of research has been done on the role of immune cells and the process of non-shivering thermogenesis or browning. In the current hypothesis it is believed that thermogenesis is activated by the joint interaction of eosinophils and type 2 Innate Lymphoid Cells (ILC2), leading to the alternative activation of ATMs, which start secreting catecholamines to induce the expression of thermogenic genes in brown adipose tissue (BAT) and lipolysis in white adipose tissue (WAT) of mice [14]. Depletion of alternatively activated ATMs impairs the thermogenic response to cold, while IL4 induces catecholamine synthesis, triglyceride lipolysis and thermogenic gene expression in adipocytes [14]. However, this hypothesis has recently been challenged, since the deletion of tyrosine hydroxylase, a key enzyme in the catecholamine synthesis pathway, in hematopoietic cells was shown to have no effect on thermogenesis upon cold exposure in mice [15]. Interestingly, another recent study showed that M1 ATMs express α4 integrin, which interacts with VCAM-1 on adipocytes of the

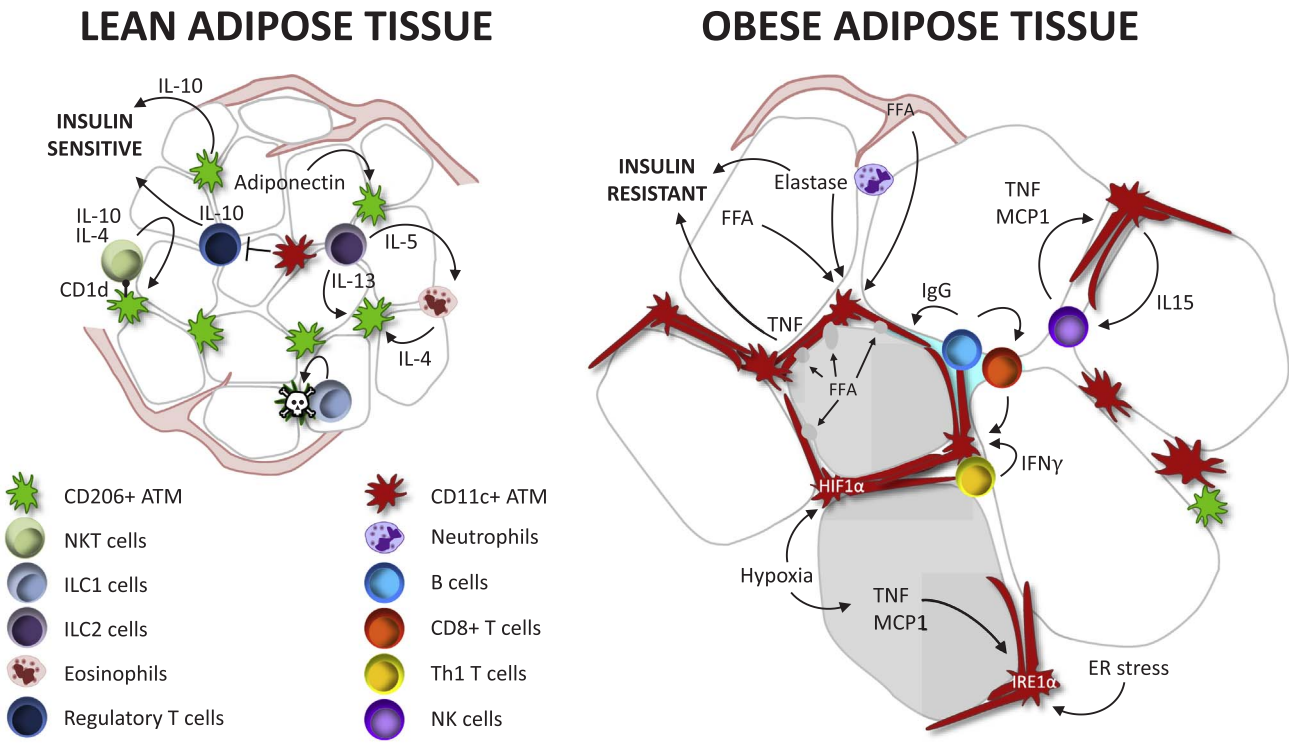

Fig. 1. The adipocyte niche influences macrophage polarization. In lean adipose tissue the adipocytes are well vascularized, insulin sensitive and healthy. Adipocytes produce factors including adiponectin to promote the alternative activation of CD206+ ATMs (green), and as a response these ATMs produce beneficial cytokines including IL-10. CD206+ ATMs present lipid antigens through their CD1d receptor to NKT cells, which stimulates their proliferation and activation. In return, NKT cells stimulate CD206+ polarization by producing IL-4 and IL-10. Regulatory T cells also produce the beneficial IL-10 and *in vitro* assays suggest that CD11c+ ATMs can inhibit Treg differentiation, leading to their reduction in obesity. In lean adipose tissue, ILC1s have recently been shown to kill damaged CD206+ ATMs. Eosinophils and ILC2s work together to stimulate M2 polarization, through the production of IL-4 and IL-5/IL-13, respectively. In obese adipose tissue, the immune landscape changes drastically with more pro-inflammatory immune cells. Also, adipocytes are hypoxic, insulin resistant and stressed. Pro-inflammatory CD11c+ ATMs (red) accumulate, due to the increased levels of FFA, pro-inflammatory cytokines, hypoxia and ER stress. These ATMs are typically found in crown like structures (CLS) around a dying adipocyte (grey). In addition, neutrophils accumulate and stimulate CD11c+ M1 polarization through the secretion of elastase. Furthermore, B cells secrete IgGs, especially around CLS, which stimulates pro-inflammatory ATM polarization, together with CD8+ T cells and IFN-γ producing Th1 T cells. Also NK cells accumulate, producing more pro-inflammatory mediators including TNF and MCP1. CD11c+ ATMs have also been found to stimulate NK cell accumulation and proliferation, through, for example, the production of IL-15. ILC1/2 (Innate Lymphoid Cells 1/2), NKT cells (Natural Killer T cells), NK cells (Natural Killer cells), FFA (Free Fatty Acids), IRE1α (Inositol-requiring enzyme 1), HIF-1α (Hypoxia-inducible factor-1).