Chapter 7

Macrophages – The Key Actors in Adipose Tissue Remodeling and Dysfunction

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Abstract

Adipose tissue (AT) is a very important endocrine and paracrine organ that regulates other tissues and organs. Dysfunction of AT leads to a wide range of disorders like obesity, insulin resistance, diabetes mellitus, cardiac disorders, tumors and others. Adipose tissue macrophages (ATMs) are the key actors in AT remodeling and dysfunction. Their role in AT dysfunction is nowadays increasingly investigated, but still their interplay and molecular mechanisms of actions have not been fully elucidated. In this chapter, we summarized the current knowledge about the role of macrophages in AT remodeling, dysfunction and related disorders and indicate the potential directions for future research.

Keywords: Adipose tissue, macrophages, tissue remodeling, adipose tissue dysfunctions

1. Introduction

Adipose tissue (AT) was previously considered to be only a fat depot. Today, it is well known that AT secretes a large number of proteins collectively termed as adipokines (adiponectin, leptin, resistin and inflammatory cytokines TNF-α, IL6, IL8, IL1, IL10, IL18 and TGF-β) that are responsible for many different processes in the body. Therefore, AT is considered to be a highly active metabolic, endocrine and paracrine organ that regulates other tissues and organs. AT is very heterogeneous and consists of different cell types such as: adipocytes, pre-adipocytes, endothelial cells, fibroblasts, mesenchymal stem cells and immune cells (mast cells, lymphocytes and macrophages). Adipose tissue macrophages (ATMs) are cells that are responsible for AT remodeling. There are two types of ATMs, M1 (classically activated) or inflammatory macrophages and M2 (alternatively activated), anti-inflammatory or reparatory macrophages. The role of ATMs in disorders such as obesity, insulin resistance, diabetes

mellitus, cardiac disorders, tumors and others is nowadays increasingly investigated, but still their interplay and molecular mechanisms of actions have not been fully elucidated. This chapter provides an overview of current knowledge about the role of macrophages in AT remodeling, dysfunction and related disorders and indicates the potential directions for future research.

2. Adipose Tissue Macrophages (ATMs)

Although adipocytes play a central role in adipose tissue (AT) remodeling, an increasing attention is directed toward adipose tissue macrophages (ATMs). Since adipose tissue remodeling is nowadays considered as chronic inflammation, ATMs and their interaction with adipocytes are key events that orchestrate the adipose tissue remodeling process.

Resident ATMs are very heterogenic population of cells that is reflected on their function in AT [1, 2]. During AT remodeling, factors that are released from AT induce the recruitment of monocytes into AT. It has been shown that most of the macrophages in AT are derived from bone marrow [3, 4].

There are two types of ATMs: M1 (classically activated) and M2 (alternatively activated) macrophages. They are characterized based on their polarization state, the expression of particular antigens [2, 5, 6] and secretion products. M1 (classically activated) macrophages, also called pro-inflammatory macrophages, are dominant type of macrophages during AT expansion and inflammation. They are characteristic of obese AT. Classically activated macrophages can be induced by LPS and the Th1 cytokine IFN-γ and express high levels of pro-inflammatory mediators including F4/80, CD11c, TNF-α, IL-6, iNOS, CCR2, IL-12 and IL-23 [6–9]. M2 (alternatively activated) macrophages, also called reparatory or anti-inflammatory macrophages, are dominant in lean AT. M2 macrophages are responsible for AT homeostasis, tissue repair and immunosuppression. Exposure of macrophages to the TH2 cytokine IL-4 produces M2 phenotype. They express F4/80, CD301, arginase 1 [6, 7] and CD163 and high levels of scavenger, mannose, and galactose-type receptors. They secrete anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist [8, 9] and are shown to inhibit NOS (iNOS) activity. M2 macrophages preserve normal adipocyte function by promoting tissue repair and angiogenesis in an increasing AT mass [2, 10].

3. The role of ATMs in adipose tissue dysfunction and related disorders

The exact role of ATMs in AT dysfunction and related disorders is still not known. In recent years, a lot of research has been done, and it has been shown that the balance between M1 and M2 macrophages is crucial for maintaining normal adipocyte function and AT homeostasis.

Obesity is a very common chronic disease that leads to the development of insulin resistance, diabetes mellitus, cardiac disorders and others [3, 4, 11–15]. Obesity is characterized as a low-

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grade chronic inflammation with unbalanced production of pro- and anti-inflammatory adipokines that contributes to the development of metabolic syndrome [4, 11–14, 16] and may be involved in a variety of physiologic and pathologic processes [17]. In obesity, the balance between M1 and M2 macrophages is disturbed and moved toward M1 inflammatory macrophages. There are two mechanisms of imbalance occurrence: infiltration of monocytes from circulation under the influence of molecules secreted from growing AT and "phenotypic switching" between M1 and M2 macrophages. During the AT growth, adipocytes secrete products that promote the production of macrophage inflammatory cytokines [18, 19]. These products influence the polarization of resident macrophages. A model of "phenotypic switching" of macrophages has been reported by Lumeng et al. in 2007 [6]. Their model emphasized that obesity is accompanied by a transformation in the polarized states of macrophages, from an "alternatively activated" M2 that primarily accumulates during negative energy balance to a more pro-inflammatory "classically activated" M1 macrophages. This phenotypic change from M2 to M1 polarization in obese adipose tissue leads to adipose tissue inflammation [20–23]. Macrophages that are infiltrated into AT from circulation are an important source of inflammation in obese AT. Chemokines are small pro-inflammatory molecules that promote macrophage mobilization from bone marrow into tissues. Increased expression of chemokines in obese adipose tissue has been implicated in the control of monocyte recruitment to the adipose tissue. During the expansion of AT, secretion of pro-inflammatory cytokines is upregulated and they are released into the circulation. It is shown that MCP-1/CCR2 pathways have pathophysiological role in macrophage infiltration into obese adipose tissue [24, 25]. MCP-1 plays a role in the recruitment of macrophages into obese adipose tissue. Increased levels of MCP-1, CXCL14, MIP-1α, MCP-2, MCP-3 and RANTES can be observed in AT of mice with genetic or DIO [15, 26]. CCR2 expressed in bone marrow cells is involved in macrophage infiltration into obese adipose tissue [27]. In addition to the MCP-1/CCR2 pathway, there are several reports suggesting the potential involvement of other chemotactic factors in obesity-induced macrophage infiltration such as osteopontin, angiopoietin-like protein 2 and CXCL14 [26, 28, 29]. Downregulation of MKP-1 is critical for increased production of MCP-1 during adipocyte hypertrophy [30]. Increased number of pro-inflammatory CD11c+ M1-like ATMs in established obesity is a result of increased monocyte migration into AT, polarization of ATMs toward the M1 and a low level of proliferation of these cells after they become ATMs [31]. Adipocyte hyperplasia and hypertrophy both contribute to the expansion of AT that leads to hypoxia, adipocyte cell death, enhanced chemokine secretion and dysregulation in fatty acid fluxes [32]. Necrosis of adipocytes is a prominent phagocytic stimulus that regulates ATMs infiltration. Macrophages aggregate around these dead adipocytes forming crown-like structures (CLSs) in advanced obesity [33–36]. Macrophages fuse to form multinucleated giant cells and to phagocyte the residual lipid droplet. They become increasingly activated in their attempt to clear the potentially cytotoxic remnant lipid droplet forming large lipid-laden multinucleated syncytia in the process, a commonly accepted hallmark of chronic inflammation [7, 33]. Macrophages aggregate to constitute a CLS surrounding dead adipocytes in advanced obesity [6, 34, 35]. Electron microscopic analysis also revealed lipid-laden phagolysosomes in macrophages within CLS [33]. It is shown that massive adipocyte death can indeed drive rapid accumulation of ATMs

as an integral element in the remodeling of fat pads [37] by using a transgenic model of inducible lipoatrophy. The number of necrotic adipocytes positively correlates with average adipocyte size in obese mice and other mouse models of adipocyte hypertrophy [33, 36, 38]. It has been suggested that macrophage localization and infiltration are strongly linked to adipose cell death [9, 33]. It is shown that adipocyte death and/or the death receptor Fas signaling contribute to obesity-induced adipose tissue inflammation and systemic insulin resistance [39, 40]. TNF-alpha induces pro-apoptotic and/or death signals in a variety of cell types, it is therefore interesting to speculate that hypertrophied adipocytes, which are stimulated and thus dying by macrophage-derived TNF-alpha, can release saturated fatty acids as an endogenous danger signal that reports their diseased state to macrophages in obese adipose tissue [4]. CCL5 production by fibroblasts, platelets and monocytes/macrophages is a particular feature of inflammatory disorders such as atherosclerosis [41, 42]. It is shown that CCL5, through CCR1 and CCR5, contributes to transendothelial migration of monocytes and T cells in atherogenic lesions [43]. CCL5 provides anti-apoptotic signals via the Akt and Erk1/2 pathways, which could then favor the scavenging role of tissue macrophages [44]. Obese adipose tissue is shown to be poorly oxygenated [45, 46]. During the expansion of AT, hypoxic areas are created due to adipocyte hypertrophy [47] that leads to the upregulated secretion of macrophage migration inhibitory factor (MIF), the matrix metalloproteinases MMP-2 and MMP-9, IL-6, Angplt4, PAI-1, VEGF and leptin [46, 48–50] that all together lead to inflammation. Leptin and VEGF are hypoxia-associated genes that are directly regulated by HIF-1, a master regulator of hypoxia and oxygen homeostasis is HIF-1 [51, 52]. Sun et al., 2011, suggest that hypoxia-induced fibrosis that follows AT inflammation may be a key factor that ultimately stimulates the local inflammatory responses [2]. Free fatty acids are stored in AT in the form of triglycerides and can cause lipotoxic side effects when are present in high amounts in tissues. During adipocytes' hypertrophy FFAs are released through lipolysis and cause inflammatory response. By increasing local extracellular lipid concentrations, FFAs lead to the accumulation of ATMs [53, 54]. FFAs may act as ligands for the TLR4 complex, like LPS [55]. Activation of TLR4 complex by saturated fatty acids may be involved in the regulation of metabolic homeostasis within the adipose tissue. FFAs contribute to the polarization of infiltrated macrophages toward M1 [4]. It is shown that M1 population of macrophages is dominant in the states of overnutrition and that inflammatory response is mediated by FFAs [7, 56].

4. The role of macrophages in tumors

The exact role of macrophages in tumor development and progression is still not fully examined, but it is shown that macrophages are associated with solid tumors. Studies performed with various tumors showed that tumor-associated macrophages (TAMs) have a lot of similarities with M2 type of macrophages with high expression of IL-10 and low expression of IL-12. The expression of CD163 is high in TAMs and is used as a reliable marker for TAMs [57, 58]. These are potential indicators that TAMs are M2 polarized macrophages [59] with potent immunosuppressive functions. It is shown that TAMs possess anti-inflammatory, pro-angiogenic and tumor-promoting properties [60] and are characteristic of the late stage of tumor progression. Adipose tissue may support breast and prostate cancer develop-

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ment and progression via secretion of pro-inflammatory cytokines. Studies performed with mammary gland-associated AT and periprostatic AT showed that secretion of pro-inflammatory cytokines is increased in surrounded AT [61].

5. Conclusions and future perspectives

Further investigations are needed to understand the molecular mechanisms by which ATMs participate in the development of various disorders, which would open the door to the findings and development of new molecular target therapies. Dalmas et al., 2015 [62], suggested that inhibition of interferon regulatory factor 5 (IRF5), transcription factor implicated in polarization of macrophages towards M1, could be a potential strategy to control pathological AT expansion in obesity and insulin resistance. Repolarization of ATMs could also be one of the possible ways of treatment, but further investigation in this direction is needed.

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