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Review

Adipose tissue macrophages

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Abstract

It is now broadly accepted that low-grade chronic inflammation associated with obesity leads to the onset of insulin resistance and type 2 diabetes mellitus. Obesity-associated inflammation is characterized by an increased abundance of macrophages in adipose tissue along with production of inflammatory cytokines. Adipose tissue macrophages (ATMs) are suspected to be the major source of inflammatory mediators such as TNF-α and IL-6 that interfere with adipocyte function by inhibiting insulin action. However, ATMs phenotypically resemble alternatively activated (M2) macrophages and are capable of anti-inflammatory mediator production challenging the concept that ATMs are simply the "bad guys" in obese adipose tissue. Triggers promoting ATM recruitment, ATM functions and dysfunctions, and stimuli and molecular mechanisms that drive them into becoming detrimental to their environment are subject to current research. Strategies to interfere with ATM recruitment and adverse activation could give rise to novel options for treatment and prevention of insulin resistance and type 2 diabetes mellitus.

Keywords: Inflammation; Insulin resistance; Obesity; Alternatively activated macrophages

1. Introduction

Obesity is associated with a chronic low-grade inflammation that predisposes to insulin resistance and development of type 2 diabetes. These chronic inflammatory alterations are associated with increased abundance of macrophages in adipose tissue (AT). AT macrophages (ATMs) probably interfere with adipocyte function, which is an important factor for systemic insulin sensitivity. Thus, ATMs appear to critically contribute to the pathogenesis of type 2 diabetes mellitus and the metabolic syndrome, an umbrella term to encompass visceral obesity, hypertension, and impaired glucose and lipid metabolism conferring risk for cardiovascular disease. Recent studies have shed light on the phenotype of human and murine ATMs. However, many molecular details underlying the recruitment of macrophages to adipose tissue and the insulin desensitizing effects of ATMs are unresolved yet. This review recapitulates the current developments in these topics. Moreover, we summarize the progress on attempts to treat insulin resistance and hence prevent type 2 diabetes by interference with ATM recruitment and activation.

2. Adipose tissue macrophages: suspected to cause type 2 diabetes mellitus

2.1. Obesity-induced chronic inflammation

Type 2 diabetes mellitus is currently one of the main health threats for humans due to the demographic increase of overweight or obese individuals and is causing enormous social an economical burdens [1]. Obesity, particularly visceral obesity that correlates with waist circumference, is one of the major risk factors to develop insulin resistance. Insulin resistance, i.e. reduced sensitivity to insulin action, is a fundamental step towards type 2 diabetes mellitus [2]. Importantly, obesity and insulin resistance are associated with a chronic low-grade inflammation as determined by increased plasma levels of C-reactive protein, IL-6, IL-8, and TNF-α in patients and different animal models of obesity [3,4]. The main origin of this systemic inflammatory response is located in adipose tissue (AT) [5]. AT produces a variety of mostly inflammatory cytokines and chemokines, collectively called adipokines, such

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as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and monocyte chemoattractant protein-1 (Mcp-1). Inflammatory adipokine expression is elevated in obesity in mice [6–8] and humans [9], whereas production of the anti-inflammatory and insulin-sensitizing adipokine adiponectin [10] is reduced with increasing body weight.

2.2. A role for macrophages in the onset of insulin resistance

AT is the largest endocrine organ in most humans and above all in obese individuals [11]. Adipocyte function critically depends on their sensitivity to insulin action to induce glucose uptake and inhibits lipolysis. The first evidence that inflammatory mediators can impede insulin sensitivity, i.e. cause insulin resistance, stems from experiments with neutralizing TNF-α antibodies in obese rats [5]. *In vitro* experiments showed that secreted factors from macrophage-like cell lines affect insulin sensitivity in adipocytes [12,13]. More detailed analyses revealed that murine macrophages alter expression of glucose transport protein 4 (GLUT4) and the insulin receptor substrate (IRS)-1 in co-cultured 3T3-L1 adipocytes, which is in part reversible by neutralizing TNF-α antibodies [14]. Also IL-1β impairs insulin signaling and action by targeting IRS-1 [15]. Additionally, IL-6 and TNF-α prevent the normal development of the murine 3T3-L1 preadipocyte cell line to fully differentiated adipocytes and promote an inflammatory adipocytes phenotype [16]. Also preadipocytes obtained from human adipose tissue treated by macrophage- and particularly ATM-conditioned medium exhibit marked inhibition of adipogenesis, as assessed by decreased cellular lipid accumulation and reduced expression of adipogenic and lipogenic genes [17].

Since adipocyte function is an important factor for systemic insulin sensitivity [18], inflammatory cytokines could be a trigger of type 2 diabetes mellitus. Because inflammatory adipokines are to the largest extent produced in obese AT predominantly by nonfat cells such as macrophages [8,19], ATMs are assumed to critically contribute to the pathogenesis of type 2 diabetes mellitus and the metabolic syndrome.

This hypothesis is corroborated by findings that obesity-associated AT inflammation is characterized by an increased abundance of ATM, as shown not only by increased macrophage gene expression in AT of diet-induced and genetically obese mice, but also by immunohistochemical identification of macrophages in the AT [7,8]. Since several studies have confirmed a correlation between body mass index (BMI, the measure of obesity) and ATM numbers particularly in the metabolically relevant visceral AT in humans [20–24], ATMs could be promising targets for prevention and treatment of insulin resistance.

2.3. The recruitment of ATMs

One of the most important questions concerning ATMs are the triggers driving the recruitment of ATMs in obesity. A plausible reason for the need of increased numbers of phagocytes is given by increased necrosis-like adipocyte cell death in rodent obesity that is probably due to detrimental effects of adipocyte hypertrophy [25]. Dead adipocytes are often found surrounded by ATMs in so-called "crown-like" structures supposed to scavenge cell debris and free lipid droplets. Also in human subcutaneous as well as visceral AT these crown-like structures can be observed exclusively in obese subjects, although at low frequency [20,23,25]. However, the signal by which adipocyte necrosis leads to increased ATM recruitment is not known. The occurrence of adipocyte death and crown-like structures in the absence of obesity in hormone-sensitive lipase mutant mice [25] suggests that metabolic alterations probably involving endoplasmic reticulum stress [26] provokes chemokine production by stressed adipocytes.

The expression of chemokines such as Mcp-1 (gene: Ccl2), Mcp-2 (Ccl8), and RANTES (Ccl5) as of chemokine receptors as Ccr2 and Ccr5 is increased in the AT of obese mice [6,7,27]. Obviously, Mcp-1 is involved in attracting monocytes to AT, since in Mcp-1 (*Ccl2*) knockout mice ATM numbers are decreased along with improved metabolic parameters after high-fat diet feeding [28]. According results have been observed in mice deficient for the Mcp-1 receptor Ccr2 [29]. Conversely, Mcp-1 overexpression in AT causes insulin resistance [28,30]. The fact that ATMs that have been newly recruited during high-fat diet feeding express more Ccr2 compared to resident ATMs [31] supports the concept that Ccr2 ligands such as Mcp-1, -2, -3 and -4 contribute to their attraction. In line with this concept, weight loss induced by bariatric surgery mediates a reduction of AT Mcp-1 expression and ATM numbers in morbidly obese patients [20]. However, in other mouse lines with targeted Ccl2 mutations including a common mouse model of genetic obesity (*ob*/*ob* mice), depletion of Mcp-1 does not affect insulin sensitivity nor AT macrophage accumulation and TNF-α expression [32,33]. Hence, the stimuli inducing Mcp-1 expression in AT as well as the role of this and other chemokines for ATM recruitment still have to be clarified.

3. The nature of adipose tissue macrophages

3.1. The M1/M2 concept of macrophage classification

Mirroring the Th1/Th2 concept of T-cell activation, a concept of M1/M2 polarization has recently been developed for macrophages. Depending on the stimuli such as cytokines and microbial products, macrophages develop into specialized cell types and exert unique functional properties [34]. Macrophages are classically stimulated by IFNγ alone or in combination with lipopolysaccharide (LPS), produce inflammatory cytokines (e.g., IL-1, IL-6, TNF-α), reactive oxygen species such as NO by iNOS activity, and are capable of inducing Th1-polarized T-cell responses. These "classical" macrophages are named M1 in contrast to "alternatively activated" M2. M2 have primarily been described to be induced by IL-4 and IL-13 [34]. Subsequently, immune complex-activated macrophages (originally named type II macrophages [35]) and IL-10-"deactivated" macrophages were included into the M2 model as distinct subtypes [36,37].