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M1 Extra Weight in the Balance: The Role of Macrophages in Obesity

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Abstract

Obesity affects millions of people worldwide and is a complex and multifactorial syndrome. Alterations in eating habits and lifestyle in developed countries increased obesity rates drastically through the past years and also the deaths associated with this condition. The immune system is an important component to maintain adipose tissue homeostasis and also to promote inflammation during obesity. In this mini review, we will briefly describe the main factors that contribute to systemic low-grade inflammation in obesity and lead to insulin resistance.

Keywords: Obesity; Macrophages; Inflammation; Adipose tissue

Introduction

Obesity is a condition characterized by excessive fat accumulation that has become a worldwide epidemic problem. According to the World Health Organization, in 2016, over 650 million adults were obese [1]. It is noteworthy that overweight and obesity are related to several diseases, such as cardiovascular diseases, diabetes and some cancers [1,2]. Another important correlation exists between obesity and the immune system, where obesity is strongly associated with systemic low-grade inflammation.

Obesity and inflammation

The link between obesity and inflammation has been studied since the 90's with the discovery that TNF-α was augmented in obesity and associated with insulin resistance [3]. From there to here, innumerous studies have demonstrated the importance of the immune system in obesity [4-8]. During obesity development, the adipose tissue functions not only as a reservoir of fat but also as an endocrine and immune organ, being capable of producing hormones, lipids, adipokines and proinflammatory cytokines [9-14].

Two important adipokines related to obesity are adiponectin and leptin. Adiponectin is an anti-inflammatory adipokine that can act on immune cells to inhibit the production of TNF-α and IL-6 and induce the production of Il-10 and IL-1RA. In line with that, adiponectin is known as an insulin sensitizer, being observed that adiponectin knockout mice have increased insulin resistance and overexpression of adiponectin can induce insulin sensitivity in diet-induced obese mice [15-17]. In contrast, leptin is considered a proinflammatory adipokine due to its actions on immune cells to promote activation, secretion of TNF-α, IL-1, IL-12, nitric oxide and downregulate the production of IL-10 [4,18-22].

Furthermore, immune cells play a major role in adipose tissue inflammation since resident and infiltrating inflammatory cells expand in the adipose tissue during obesity and take part on systemic inflammation due to their production of TNF-α, IL-6, IL-1β and other factors [23,24].

Macrophages, obesity and insulin resistance

Macrophages are important players in innate immunity and also in the context of systemic low-grade inflammation associated to obesity. The finding that monocytes infiltrate the adipose tissue and differentiate into macrophages was an important step to unveil the role of macrophages in obesity and its associated inflammation [23,25,26].

Macrophages can be subdivided in two main subtypes: M1 and M2 macrophages. M1 or classically activated macrophages are induced by IFN-γ and LPS, and produce mainly proinflammatory cytokines, as TNF-α and IL-6, while M2 or alternativelyactivated macrophages are induced by IL-4 and produce primarily IL-10 [27,28]. Because of their production of proinflammatory cytokines, M1 macrophages are associated with the promotion of Th1 response, microbicidal activity, tissue

injury, enhanced glycolysis and tumor suppression. On the other hand, M2 macrophages orchestrate tissue repair/remodeling and promote angiogenesis and tumor progression [29-31].

Both M1 and M2 macrophages can be found in the adipose tissue, with increased numbers of M2 macrophages in lean conditions [32]. In normal weight, the lean adipose tissue microenvironment is associated with either increased levels of adiponectin, which enhances insulin sensitivity and increases M2 polarization, and with increased number of regulatory T cells that also promote M2 differentiation through the production of IL-10 and TGF-β and maintain tissue homeostasis [33-35]. However, in obese conditions, the ratio between M1/M2 shifts toward a proinflammatory profile, with infiltration of monocytes that differentiate into M1 macrophages in the adipose tissue [32]. These proinflammatory macrophages have unique surface markers, as CD11c, and respond to cytokines, free fatty acids, triglycerides, leptin, retinol-binding protein 4 (RBP4) and other factors present in the obese adipose tissue milieu [6,9,36,37]. During obesity, several proinflammatory pathways are triggered in both macrophages and adipocytes, as the c-Jun NH2-terminal kinase (JNK 1 and 2) [38], extracellular signal-regulated kinase 1 and 2 (ERK 1 and 2) [39], inhibitor of κB kinase (IKK) [40] and mitogen-activated protein kinase p38 (p38 MAPK), which are responsible for alterations in the insulin receptor signaling pathwaysthat lately contribute to insulin resistance [8,41]. Toll-like receptors (TLRs) and inflammasomes are also important components for the inflammatory response in the adipose tissue. During obesity, increased expression of TLRs and inflammasomes in adipose tissue macrophages enhances the secretion ofTNF-α and IL-1β, which further exacerbate inflammation [42-44]. TLRs can signal through an adaptor molecule called Myd88 (for myeloid differentiation primary response gene 88) and recently, Castoldi and colleagues described a new role for Myd88 in obesity and insulin resistance [45]. They demonstrated that in the absence of Myd88 there is an upregulation of dectin-1 in adipose tissue macrophages, which correlates with exacerbated obesity and increased insulin resistance [45]. In this sense, treating mice with dectin-1 inhibitor decreased M1 macrophages in the adipose tissue and ameliorated insulin resistance [45]. Still, in the context of TLR signaling pathway, for several years it was believed that TLR4 could be activated by saturated fatty acids, which triggered macrophage activation and contribute to adipose tissue inflammation during obesity [43,46-48]. Nevertheless, Lancaster and colleagues recently demonstrated that the inflammatory fatty acid palmitate is actually not a TLR4 agonist; instead, palmitate induces macrophage activation by altering macrophage metabolism [49].

Several components in the immune system influence the development of obesity and insulin resistance. However, obesity is a complex and multifactorial disease and the immune system is regulated by an intricate network of pathways cell interactions. Thus, the study of this network is still needed to unveil new concepts and paradigms.

Conclusion

Obesity is a relevant healthy issue that affects millions of people worldwide and leads to high morbidity and mortality with high costs to healthy systems. The immune system and specially macrophages are main players in aggravating obesity and inducing insulin resistance. Considerable studies were performed to elucidate the mechanisms by which immune cells, adipocytes and other factors work together to promote tissue inflammation. The understanding of adipose tissue physiology in lean and obesogenic conditions may lead to the development of new strategies and treatments for obesity and its-associated comorbidities.

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