Review

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Role of interleukins in obesity: implications for metabolic disease

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It has been two decades since the discovery that pro-inflammatory cytokines are expressed in obesity. This initial work was the catalyst for the now-accepted paradigm that nutrient overload promotes inflammation and links the metabolic and immune systems, where inflammation may be pathological. However, inflammation is an adaptive and, importantly, an energy-consuming process. Indeed, the rapid mobilization of stored energy reserves by cytokines such as the interleukins, is critical to mounting any successful inflammatory response. Thus, the role of the interleukins in metabolism and energy homeostasis is more complex than first thought and recent evidence is mounting that, for several interleukins, although excess production is negative, blockade or insufficiency is equally undesirable.

Introduction

Diabetes and inflammation have been linked for over 100 years with the observation that treatment with high doses of nonsteroidal anti-inflammatory drugs decreased glucosuria in patients presumed to have type 2 diabetes mellitus (T2DM) (reviewed in [1]). The concept that inflammation and metabolic disease were associated gained momentum during the mid-20th century [2,3], but the definitive evidence linking inflammation to obesity and nutrient overload came 20 years ago, when Hotamisligil and colleagues made the seminal observation that mRNA of the proinflammatory cytokine tumor necrosis factor alpha (TNFα) was highly expressed within adipose tissue in several rodent models of obesity and, when TNFα was neutralized, insulin action was enhanced [4]. Further studies by this group demonstrated that genetically obese *ob*/*ob* mice with targeted mutations in TNF receptors display an improved insulin sensitivity relative to *ob*/*ob* control mice [5]. These studies stimulated a paradigm shift in our understanding of the nature of metabolic disease and acted as a catalyst for the new field of research now known as 'immunometabolism'.

Although the discovery regarding TNFα was key to the immergence of the field of immunometabolism, the subsequent identification implicating two key molecules downstream of the transmembrane TNF receptors, namely the inhibitor of kappa B kinase (IKK) and c-Jun NH_2-terminal kinase (JNK), were critical in our understanding, and linked nutrient overload, obesity, and impaired insulin action via signaling events. IKK has an essential role in the activation of nuclear factor κB (NF-κB), a family of transcription factors responsible for the induction of inflammatory genes and implicated in innate immunity [6]. However, work principally driven by Shoelson and colleagues, has demonstrated IKK to be implicated in obesity-induced insulin resistance. Heterozygous IKKβ-deficient mice either fed a high-fat diet or crossed with *ob*/*ob* mice, display improved metabolic homeostasis compared with appropriate control mice [7]. Subsequent studies confirmed the important role that the activation of IKKβ has in mediating obesity-induced insulin resistance, given that liver-specific overexpression of IKKβ rendered the animal insulin resistant, whereas suppression of IKKβ in this organ reversed the phenotype [8]. JNK is a member of the mitogen-activated protein kinase (MAPK) family and is essential for cells to respond to changes in environment [9]. Three genes encode the JNK proteins; *JNK1* and *JNK2* are ubiquitously expressed, whereas *JNK3* has a limited expression pattern. As discussed, it is clear that metabolic diseases are associated with chronic elevations in various inflammatory molecules, including cytokines, acute phase proteins, and free fatty acids (FAs) [1]. Given that these molecules are potent activators of JNK, it is not surprising that JNK is activated by nutrient oversupply and that JNK1-deficient ($JNK1^{-/-}$) mice displayed reduced adiposity and increased insulin sensitivity compared with littermate controls following a high-fat diet [10]. In addition, mice with JNK1 deficiency in adipose tissue display suppressed high-fat diet-induced insulin resistance in the liver [11].

As discussed above, both IKK and JNK are serine kinases that induce inflammation by the activation of the transcription factors NF-κB and activator protein 1 (AP-1), respectively. In mediating insulin resistance, it is likely that IKK and JNK operate via two predominant mechanisms; those being the transcriptional upregulation of proinflammatory genes and the phosphorylation of phosphoacceptor residues on insulin signaling molecules [1]. Effective insulin signaling is dependent upon tyrosine phosphorylation of the insulin receptor and the insulin receptor substrates (IRS) immediately downstream. By contrast, phosphorylation of specific serine residues within IRS molecules inhibits insulin signaling. It is well accepted that both IKKβ and JNK physically associate with IRS1

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and phosphorylate Ser^{307}, resulting in the inhibition of insulin signaling [12]. Hence, the phosphorylation of key inhibitory residues within IRS1/2 by IKK and JNK appears to be the critical pathway by which these molecules induce insulin resistance in insulin-sensitive tissues.

However, this direct effect of these serine threonine kinases on insulin action is not the sole pathway by which they exert their effect. Interestingly, treatment of liver-specific IKK β overexpressing mice with an interleukin 6 (IL-6)-neutralizing antibody improved insulin resistance [8]. Likewise, JNK1-dependent secretion of IL-6 by adipose tissue increased the expression of Suppressor of cytokine signaling-3 (SOCS3) in liver, leading to hepatic insulin resistance [11]. These studies implicate IL-6 in the etiology of insulin resistance, but as subsequently discussed, to conclude that IL-6 results directly in insulin resistance in all circumstances is an oversimplistic conclusion.

IL-6 is just one of several 'interleukins'. The term 'interleukin' has been used to describe a group of cytokines (so-called because they are secreted proteins) with complex immunomodulatory functions in white blood cells. These functions include cell proliferation, maturation, migration, and adhesion [13]. Hence, the primary function of the interleukins is to initiate an immune response by binding to high-affinity receptors located on the surface of cells. In this respect, interleukins act in a paracrine or autocrine fashion [13]. However, it is now clear that interleukins are not only a component of the immune system, but are also secreted by many different cells within the body, some of which have major roles in the etiology of metabolic diseases, such as T2DM [14]. Here, I discuss in detail the role of the interleukins with respect to nutrient oversupply and metabolic homeostasis.

Role of the IL-1 family of cytokines and NRLP3 inflammasome in metabolic disease

The IL-1 family of ligands and receptors has been associated with the pathogenesis of acute and chronic inflammatory disorders more than any other cytokine family [15]. During the mid-1980s, two discrete, but interconnected complementary DNAs encoding proteins sharing IL-1 activity were isolated from a macrophage cDNA library, defining the first two individual members of the IL-1 family (IL-1α and IL-1β) [16,17]. Since then, a further ten members of the IL-1 family have been identified: IL-1Ra, IL-18, IL-33, IL-36Ra, IL-36α, IL-36β, IL-36γ, IL-36Ra, IL-37, and IL-38 [15].

IL-1β, inflammasomes, and β cell destruction: therapeutic implications

Although type 1 diabetes mellitus (T1DM) and T2DM are different diseases, several lines of evidence exist that link the two diseases. For example, the prototypical mouse model of T1DM, the nonobese diabetic (NOD) mouse, is susceptible to insulin resistance [18], whereas obesity, which strongly predicts T2DM, is also linked to the susceptibility of developing T1DM [19]. It is unequivocal that both diseases are characterized by β cell destruction [20]. The molecular mechanisms that lead to β cell destruction in T1DM are reasonably well defined because T1DM is an autoimmune disorder [21]. However, the mechanisms that lead to β cell destruction in T2DM are less well understood. Given that insulin resistance precedes fulminant T2DM, it is clear that hyperinsulinemia, or β cell hypersecretion of insulin, is followed by deterioration of β cell function and β cell death through apoptosis [22]. The precise initiator of β cell apoptosis is the subject of debate, but it has become quite apparent that IL-1β is a key cytokine in the etiology of T2DM because it has been implicated in both β cell dysfunction and death [23]. Pancreatic sections obtained from patients with T2DM stain positive for IL-1β, whereas high glucose levels increase β cell IL-1β production *in vitro* [24]. In a seminal paper published by Donath and colleagues, the authors demonstrated that the blockade of IL-1β with anakinra (a recombinant human interleukin-1-receptor antagonist), improved glycemia and β cell secretory function and reduced markers of systemic inflammation in patients with T2DM [25]. This work laid the foundation for the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS). The CANTOS trial is currently underway and will test the efficacy of canakinumab, a monoclonal antibody targeting IL-1β for cardiovascular disease and T2DM, in over 17 000 patients [26]. Therefore, it is clear that factors controlling the secretion and/or signaling of bioactive IL-1β have major therapeutic implications for the treatment of T2DM.

The production of IL-1β is a highly regulated process. The transcription of IL-1β is initiated through the activation of pattern recognition receptors, such as Toll-like receptors (TLRs). However, once the protein is translated, pro-IL-1β is biologically inactive and requires processing to generate the active form that is secreted. This process is reliant on caspase 1, which itself requires processing to form the active enzyme. The activation of caspase 1 is mediated by high-molecular-weight protein complexes termed 'inflammasomes' [27]. Inflammasomes are molecular platforms that principally comprise the interaction of Nod-like receptor proteins (NLRPs) and the adaptor molecule apoptosis-associated spec-like protein containing a caspase recruitment domain (CARD). Several inflammasomes have been identified, including NLRP1, NLRP3, NLRC4, ICE protease-activating factor (IPAF), and absent in melanoma 2 (AIM2) inflammasomes. Activation of all these complexes results in the production of IL-1β [27]. However, each inflammasome is differentially activated. A study by the O'Neill laboratory demonstrated the importance of the NLRP3 inflammasome in the etiology of β cell destruction [28]. This group demonstrated that oligomers of islet amyloid polypeptide (IAPP), a protein that forms amyloid deposits in the islets during T2DM, triggered the NLRP3 inflammasome and generated mature IL-1β in macrophages [28]. In addition, mice transgenic for human IAPP had more IL-1β in pancreatic islets, which localized together with amyloid and macrophages [28]. In complimentary studies from the Verchere laboratory, the authors demonstrated that human IAPP contributed to islet inflammation by recruiting and activating macrophages [29]. These findings are potentially important because they raise the possibility that drugs with selectivity for NRLP3, rather than IL-1β *per se*, may block β cell destruction without compromising the innate immune response. Of note, the O'Neill group appears to have uncovered such