Review

CellPress

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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Keywords: interleukins; inflammasome; beta cell; nutrient overload.

1043-2760/$ – see front matter
 http://dx.doi.org/10.1016/j.tem.2014.02.004

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

a candidate molecule. In a screen for inhibitors of IL-1β, a novel class of sulfonylurea-containing compounds were identified and termed 'cytokine-release inhibitory drugs' (CRIDs). One such CRID CP-456,773 ('CRID3') was recently tested in primary bone marrow-derived macrophages (BMDM) [30]. CRID3 was found to inhibit the NLRP3 inflammasome, but not other inflammasomes, such as AIM2 and NLRC4 [30]. Moreover, CRID3 was not only highly specific for the NLRP3 inflammasome, but also extremely potent, with an IC_{50} of approximately 10 nM [30]. In summary, the role of IL-β in β cell biology and the etiology of T2DM is most important and we await the results of the CANTOS trial with much anticipation.

The inflammasome, nutrient overload, and obesity-related disorders

As discussed above, the inflammasome and IL-1β are a therapeutic target for β cell destruction in T2DM, but evidence is immerging that the inflammasome is linked to obesity-related diseases, such as insulin resistance [31–33]. The pathogenesis of insulin resistance is a well-investigated area, yet the precise causes are still not fully elucidated. However, extensive evidence suggests that defects in FA metabolism and concomitant lipid accretion in key metabolic organs, such as the skeletal muscle and liver, have a major role in initiating insulin resistance [34]. One such deleterious lipid that is known to accumulate in these tissues and cause insulin resistance is ceramide. Ceramide is a potent lipid-signaling molecule that can cause insulin resistance by inhibiting the ability of insulin to activate the insulin signal transduction pathway [35] and/or via the activation of JNK [36]. Importantly, preventing ceramide accumulation by inhibiting *de novo* ceramide synthesis protects against the development of insulin resistance [37,38]. These observations support the hypothesis that increases in ceramide are an important mechanism underlying the development of muscle insulin resistance and, therefore, targeting pathways to prevent ceramide accumulation may be a viable therapeutic approach. However, recent work links the inflammasome to the deleterious effects of ceramide in nutrient overload. Vandanmagsar *et al.* [39] demonstrated that, although ceramide can activate caspase 1 and the release of IL-β in wild type mice, this process did not occur in NLRP3-deficient ($NLRP3^{-/-}$) mice. In effect, these data highlight that the NLRP3 inflammasome senses obesity-related danger signals and contributes to the etiology of insulin resistance. In addition to these recent data, other studies also implicate the inflammasome in obesity. This finding has been supported by work from an independent group who observed that $NLRP3^{-/-}$ mice displayed reduced hepatosteatosis, adipose tissue inflammation, and adiposity compared with wild type mice in conditions of nutrient overload [40]. The reduced adiposity observed in the $NLRP3^{-/-}$ mice is likely due to the role of caspase 1 in the process of adipocyte differentiation [41]. It is important to note that, in this study, at least part of the effects of the NLRP inflammasome were attributed to the production of IL-1β, because IL-1 β-deficient mice also displayed improved metabolic homeostasis in obesity [41]. Therefore, it is clear from these recent data that IL-1β is not only important for the β cell, but may also be a therapeutic avenue for the treatment of insulin resistance (Figure 1).

The paradoxical role of IL-18

As discussed above, IL-18 is a member of the IL-1 family of cytokines. Approximately 18 kDa, IL-18 is widely expressed in many mammalian cells and/or tissues including liver, adipose tissue, skeletal muscle, pancreas, brain, and endothelium [42]. IL-18 is best known for its role in inflammation, because inflammasome activation leads to caspase 1 mediated cleavage of pro-IL-18 into mature IL-18. IL-18 subsequently signals via a heterodimer of the transmembrane IL-18 receptors (α and β), and a TLR signaling cascade, eventually resulting in the activation of NFκB [43]. Studies in $NLRP3^{-/-}$ mice demonstrated, unsurprisingly, that IL-18 production was reduced in these mice and this was associated with improved metabolic homeostasis in conditions of nutrient overload [39], implicating IL-18 as a potential mediator of insulin resistance in the context of obesity induced-inflammation. In support of this notion, IL-18 is elevated in the blood of obese humans [44] and in patients with T2DM [45]. However, as alluded to earlier, complete blockade of key inflammatory cytokines may be undesirable for the maintenance of metabolic homeostasis and this, indeed, appears to be the case for IL-18. Work from two different laboratories demonstrated that IL-18 deficient ($IL\text{-}18^{-/-}$) mice become obese and insulin resistant, whereas treatment with recombinant IL-18 rescued the phenotype [46,47]. These studies ascribed the mechanism of action of IL-18 in modulating nutrient homeostasis to be central in nature through increased food intake [46,47]. However, in the study by Netea *et al.* [46], the authors demonstrated that $IL\text{-}18^{-/-}$ mice exhibited reduced insulin sensitivity and that IL-18 signaled via Signal transducer and activator of transcription 3 (STAT3) in the liver. These findings have been supported by a more recent study that demonstrated that $IL\text{-}18^{-/-}$ mice have exacerbated nonalcoholic fatty liver disease [48]. Of note, STAT3 has a major role in maintaining metabolic homeostasis in the liver [49]. STAT3 has also been shown by several groups to result in the activation of the fuel-sensing kinase AMP kinase (AMPK) to enhance fat oxidation in skeletal muscle, thereby attenuating high-fat diet-induced insulin resistance (reviewed in [50]). Unsurprisingly, recent studies demonstrate that IL-18 is implicated in metabolic homeostasis, inflammation, and insulin resistance via mechanisms involving the activation of AMPK in skeletal muscle [51]. In this recent study, IL-18 receptor-deficient ($IL\text{-}18R^{-/-}$) mice showed increased weight gain, lipid deposition in skeletal muscle, enhanced inflammation, and reduced AMPK signaling in skeletal muscle [51]. Moreover, *in vivo* electroporation of IL-18 into skeletal muscle activated AMPK and concomitantly inhibited high-fat diet-induced weight gain [51]. Together, these studies highlight the intricate balance between excessive inflammation and complete blockade of inflammatory pathways in the maintenance of metabolic homeostasis.

IL-33: a new player in obesity and metabolic disease?

IL-33 was fully characterized during the mid-2000s as a cytokine with close sequence homology to IL-18, but which signals through interleukin 1 receptor-like 1, also known

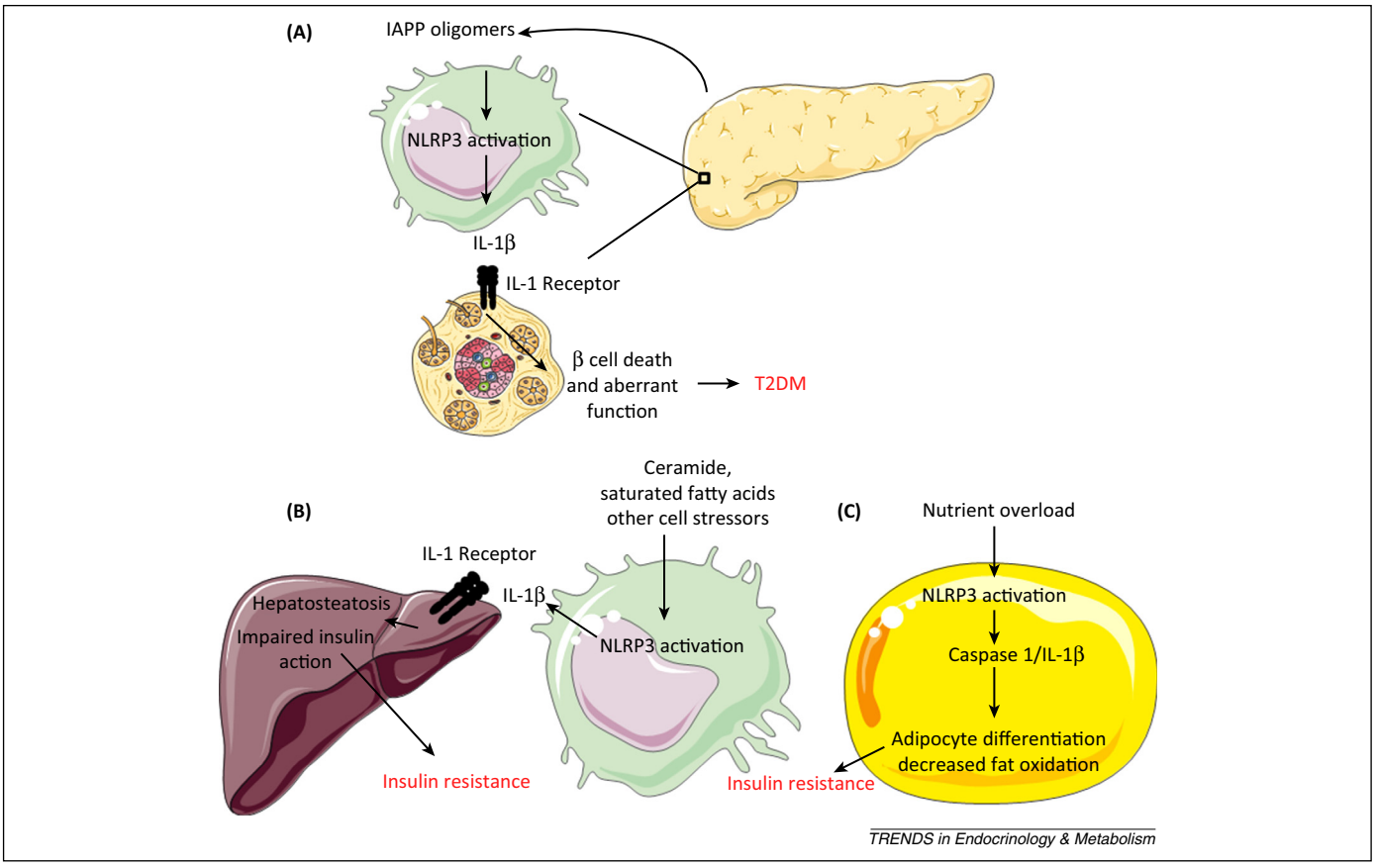

Figure 1. Role of the Nod-like receptor protein 3 (NLRP3) inflammasome and interleukin (IL) 1β in metabolic disease. Islet amyloid polypeptide (IAPP) produced by the islets can activate the NLRP3 inflammasome in macrophages and dendritic cells to release IL-1β, which can signal through its receptor on β cells to lead to cell death, compromised insulin secretory capacity, and type 2 diabetes mellitus (T2DM) **(A)**. In addition, factors associated with obesity and nutrient oversupply, such as ceramide and saturated fatty acids, can also activate the NLRP3 inflammasome in macrophages to release IL-1β, which can signal through its receptor in metabolically relevant tissues, such as the liver, to increase hepatosteatosis and impair liver insulin action, leading to insulin resistance **(B)**. Moreover, obesity can lead to NLRP3 inflammasome activation in the adipose tissue, activating caspase 1 and increasing IL-β production, adipocyte differentiation and insulin resistance, and decreasing fat oxidation.

as ST2L [52]. It appears that pro IL-33 has anti-inflammatory properties, but mature IL-33, produced by inflammasome processing, is proinflammatory [52]. Whether IL-33 is pro- or anti-inflammatory also depends on the particular disease and/or model being studied [52]. Recent studies identified that IL-33 is expressed in both human adipocytes and pre-adipocytes [53]. Akin to the paradox of IL-18, a recent important study suggests that IL-33 has a protective, rather than deleterious, role in metabolic homeostasis. Miller *et al.* [54] reported that that administration of recombinant IL-33 to *ob*/*ob* mice led to reduced adiposity, reduced fasting glucose, and improved glucose and insulin tolerance. Moreover, mice lacking endogenous ST2, a member of the Toll-interleukin 1 receptor (TIR) superfamily that does not activate NFκB, had increased body weight and fat mass and impaired insulin secretion and glucose regulation when fed a high-fat diet. Therefore, akin to IL-18, IL-33 may have a protective role in the development of adipose tissue inflammation during obesity.

The role of IL-6 in metabolic homeostasis

The IL-6 family, also known as 'long type I' or 'gp130 cytokines' comprises IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OsM), cardiotrophin 1 (CT-1), ciliary neurotrophic factor (CNTF), and cardiotrophin-like cytokine (CLC) [55]. As discussed above, obesity results in the secretion of inflammatory cytokines, including IL-6, from macrophages and/or adipocytes [56]. Given this observation, along with the fact that circulating IL-6 is elevated in obesity and metabolic disease [57], it is generally thought that elevations in the plasma and/or tissue concentrations of IL-6 have a negative effect on metabolism. This conclusion is not without foundation given that several studies, both *in vitro* [58,59] and *in vivo* [60,61], demonstrate that IL-6 is capable of inducing insulin resistance. However, whether IL-6 has positive or negative effects has become the subject of controversy [62,63], especially since the discovery that IL-6 is produced and released by skeletal muscle cells in response to concentric, nondamaging muscle contraction [64–66], because insulin sensitivity is enhanced in the immediate postexercise period [67]. Moreover, IL-6 released from skeletal muscle during contraction was found to participate in tissue crosstalk with the liver [68], adipose tissue [69] and, more recently, the gut [70], pancreas [70], and brain [71]. These earlier discoveries [64–66] were seminal in some respects because they identified skeletal muscle as an endocrine organ capable of producing 'myokines'. Approximately a decade on, the 'myokinome' is growing exponentially [72].

Notwithstanding the identification of IL-6 as a muscle secretory factor, its role in metabolic homeostasis has been largely defined by mouse genetic studies. In a landmark

study, Wallenius *et al.* [73] described a mature-onset obesity that was associated with decreased glucose tolerance in IL-6 deficient (IL-$6^{-/-}$) mice. Although this finding was challenged by others [74], a more recent study supports the hypothesis that IL-$6^{-/-}$ mice develop not only obesity, but also glucose intolerance and insulin resistance [75]. Moreover, IL-$6^{-/-}$ mice developed an increased hepatic insulin resistance and increased liver inflammation in response to a high-fat diet [75]. This study was consistent with data from the Bruening laboratory, in which the authors addressed the effect of blocking IL-6 signaling specifically in hepatocytes by disruption of the IL-6 receptor (IL-6Rα) [76]. Mice lacking the IL-6Rα on hepatocytes displayed increased systemic inflammation, mainly by enhanced secretion of inflammatory cytokines by Kupffer cells. This increased inflammation triggered systemic impairment of insulin action in the hepatocyte-specific IL-6Rα-deficient animals [76]. Akin to IL-18, IL-6 activates STAT3, which as discussed above can lead to the activation of AMPK. Indeed, the anti-obesity effect of IL-6 is likely to be due to its ability to activate AMPK [77,78]. Of note, administration of other IL-6 family cytokines, namely CNTF, also activates STAT3 and AMPK, leading to protection against high-fat feeding-induced obesity and insulin resistance [79]. However, it should be noted that the mechanism by which IL-6 can prevent obesity-induced insulin resistance is not exclusively via AMPK because the White laboratory have demonstrated that transgenic mice with sustained elevated circulating IL-6 display enhanced central leptin action and improved nutrient homeostasis, leading to protection from diet-induced obesity [80]. Although the role of IL-6 in the etiology of insulin resistance remains controversial, it appears that, on balance, IL-6 is a cytokine with generally positive effects on metabolism.

Other cytokines: IL-10, IL-13, and IL-15

IL-10 is a regulatory cytokine with pleiotropic effects on numerous cell types that express IL-10 receptor 1 (IL-10R1) and IL-10 receptor 2 (IL-10R2) and has an important and well-characterized role in regulating the immune response [81]. Along with IL-4 and IL-13, IL-10 is classically known as an anti-inflammatory cytokine. The principal function of IL-10 appears to be to limit and ultimately terminate the inflammatory response [82]. IL-10 can also reduce inflammatory cytokine activity through stimulation of soluble TNF-α receptor and IL-1R antagonist release [82]. In terms of metabolism, there is a paucity of research. However, acute IL-10 infusion can improve insulin sensitivity and signaling in mice co-infused with lipid or supraphysiological doses of IL-6 [60]. IL-10 is also a protective factor against high-fat diet-induced insulin resistance in liver [83]. Recently, IL-10 overexpression in mice via hydrodynamic delivery of the cytokine prevented weight gain and impaired glucose tolerance in animals fed a high-fat diet [84]. Moreover, in this study, IL-10 overexpression prevented macrophage infiltration into adipose tissue [84]. Therefore, somewhat surprising was the observation that neither inflammation nor diet-induced obesity and insulin resistance were exacerbated by the deletion of hematopoietic cell-derived IL-10 in mice [85]. Interestingly, however, in this study, IL-10 expression in liver and/or adipose issue was markedly elevated in mice lacking IL-10 in immune cells [85], suggesting that these tissues upregulate IL-10 in a compensatory fashion.

Similar to IL-10 and IL-4, IL-13 is T helper type 2 (Th2) cytokine that mediates macrophage alternative activation [86], which is well known to have a role in adipose tissue inflammation and altered metabolic homeostasis in response to nutrient overload [87]. However, recent evidence suggests that IL-13 has a direct role in maintaining glucose homeostasis during obesity. Similar to IL-10 [86], but in contrast to IL-4, IL-13 is expressed in appreciable amounts in the liver and adipose tissue of mice [88]. More importantly, work from the same group demonstrated that the maintenance of glucose homeostasis and insulin action is dependent on IL-13 [89]. These authors demonstrated that IL-13-deficient (IL-$13^{-/-}$) mice became glucose intolerant and insulin resistant, even on a chow diet, a phenotype that is exacerbated by high-fat feeding [89]. Moreover, similar to IL-6 and IL-18, the positive metabolic effects of IL-13 appear to be dependent upon the activation of STAT3, given that the ability of IL-13 to suppress gluconeogenic gene expression in the liver was STAT3 dependent [89]. Finally, in recent studies, Krook and colleagues demonstrated that IL-13 adds to the growing list of myokines, because it is synthesized and released from human skeletal muscle to increase skeletal muscle glucose uptake via insulin signaling [90]. Moreover, in this recent study, circulating IL-13 was lower when comparing patients with T2DM with control humans, which correlated with increased expression of the miRNAs let-7a and let-7d, which are direct translation repressors of IL-13, in the skeletal muscle from patients with T2DM [90].

IL-15, a cytokine with structural similarity to IL-2, signals through a complex comprising IL-2/IL-15 receptor β chain (CD122) and the common γ chain (gamma-C, CD132). Although best known for its secretion by mononuclear phagocytes following viral infection [91], IL-15 is known to be expressed in human skeletal muscle [92]. Moreover, it has anabolic effects in muscle tissue, where it is highly expressed and increased in response to resistance [93] and endurance [94] training. Importantly, IL-15 has also been suggested to have a role in reducing adipose tissue mass. Administration of IL-15 in rats [95] or muscle-specific transgenic overexpression in mice that results in increased circulating IL-15 concentration [96] reduced adiposity. It appears that this may be a direct effect of IL-15 because the latter reduces incorporation of lipids in adipose tissue and increases lipid oxidation [97]. Two recent studies provide further evidence that IL-15 may have a positive effect on metabolic homeostasis [98]. High fat-fed mice treated with IL-15 via adenoviral delivery, displayed weight loss and improved glucose homeostasis, compared with mice treated with a vector control [99]. More importantly, IL-15 may selectively target visceral rather than subcutaneous fat. In a separate study where skeletal muscle of mice overexpressed IL-15 via electroporation, trunk fat mass, but not subcutaneous fat mass, was reduced irrespective of diet [98]. This result appears to have human relevance because plasma IL-15 levels correlated with trunk fat mass in a large human cohort [98].

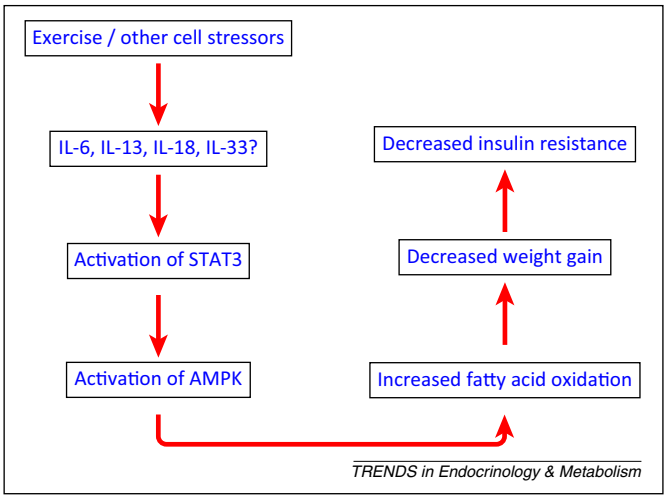

Figure 2. Role of interleukins (ILs) in maintaining energy balance. Cellular stressors, such as exercise, can increase the production of certain interleukins, such as IL-6, IL-13, IL-18, and possibly IL-33. These interleukins can activate the fuel-sensing kinase AMP kinase (AMPK), possibly via the activation of Signal transducer and activator of transcription 3 (STAT3). The increased activity of AMPK increases fatty acid oxidation, decreasing weight gain and insulin resistance. Therefore, blocking the production of these cytokines may not necessarily be advantageous for metabolic disease, despite the fact that they are considered to be pro-inflammatory.

Concluding remarks and future perspectives

Clearly, inflammation is an adaptive and energy-consuming process, and the one interleukin that could be targeted therapeutically without severe complications is IL-1β. However, it appears that most efforts should center upon selective targeting of the NLRP3 inflammasome, both for the treatment of β cell failure and in insulin resistance, where the deleterious actions of ceramide and inflammation prevail. For cytokines such as IL-6, IL-13, IL-18, and IL-33, evidence is mounting that the mobilization of stored energy reserves is critical to mounting an inflammatory response. Therefore, largely via the activation of STAT3 and downstream AMPK, the activation rather than the blockade of these cytokines has positive effects on metabolic homeostasis in situations of nutrient overload (Figure 2). In conclusion, similar to all biological processes, some activation of the interleukins appears necessary to maintain the energy balance.

Acknowledgments

I would like to thank all my current and past staff and collaborators who have contributed to this body of work. I also gratefully acknowledge the Australian Research Council and National Health and Medical Research Council (NHMRC) for continued funding support. M.A.F. is a Senior Principal Research Fellow of the NHMRC.

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