Seminars in Immunopathology (2019) 41:491–499
https://doi.org/10.1007/s00281-019-00747-2

REVIEW

The role of interleukin-6 in glucose homeostasis and lipid metabolism

Louise Lang Lehrskov[1] · Regitse Højgaard Christensen[1]

Received: 3 April 2019 / Accepted: 11 April 2019 / Published online: 17 May 2019

Abstract

Low-grade inflammation is recognized as an important factor in the development and progression of a multitude of diseases including type 2 diabetes mellitus and cardiovascular disease. The potential of using antibody-based therapies that neutralize key players of low-grade inflammation has gained scientific momentum as a novel therapeutic strategy in metabolic diseases. As interleukin-6 (IL-6) is traditionally considered a key pro-inflammatory factor, the potential of expanding the use of anti-IL-6 therapies to metabolic diseases is intriguing. However, IL-6 is a molecule of a very pleiotropic nature that regulates many aspects of not only inflammation but also metabolism. In this review, we give a brief overview of the pro- and anti-inflammatory aspects of IL-6 and provide an update on its role in metabolic regulation, with a specific focus on glucose homeostasis and adipose tissue metabolism. Finally, we shall discuss the metabolic implications and clinical potential of blocking IL-6 signaling, focusing on glucose homeostasis and lipid metabolism.

Introduction

During the past two decades, a growing body of evidence shows that low-grade inflammation is a crucial factor in the development and progression of a cluster of diseases, e.g., type 2 diabetes mellitus (T2DM) and cardiovascular disease [1]. In patients with low-grade inflammation, circulating levels of interleukin-6 (IL-6) are often increased and have been associated with detrimental metabolic actions [2]. However, a large number of contrasting studies indicate that chronically elevated IL-6 may have beneficial metabolic effects [3]. These conflicting opinions highlight the complexity of the IL-6 molecule, and it is still debated whether IL-6 is "a bad or a good guy" in the regulation of metabolism.

Moreover, a great deal of our knowledge regarding the metabolic effects of IL-6 is based on correlational studies, in vitro cell culture studies of supraphysiological concentrations of IL-6, and studies performed in rodents. Bearing in mind that there seem to be important species-specific differences, particularly of the glucose regulatory actions of IL-6, caution should be taken when conclusions are made based on data from rodent studies.

In this review, we will introduce the pleotropic molecule IL-6 and provide a brief overview of its role in different contexts where it is increased (acute and chronic inflammation and exercise). Moreover, we will discuss the complex role of IL-6 in the regulation of metabolism, with a specific focus on glucose homeostasis and adipose tissue metabolism. Finally, we shall discuss the metabolic implications of blocking IL-6 signaling and the clinical potential of IL-6 receptor blockade, focusing on glucose homeostasis and lipid metabolism.

Interleukin-6 signaling

IL-6 was identified in 1989 and is part of the IL-6 family of cytokines that include IL-11, oncostatin M, leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin-1, and cardiotrophin-like cytokine [4]. IL-6 is produced by immune cells, chondrocytes, osteoblasts, endothelial cells, skeletal muscle cells, smooth muscle cells, pancreatic islet β-cells, among several other cell types [4]. Of note, IL-6 is furthermore a myokine and an adipokine as it is secreted from skeletal muscle in response to exercise and from adipose tissue, respectively [5, 6].

This article is a contribution to the special issue on Inflammation and Type 2 Diabetes - Guest Editor: Marc Y. Donath

✉ Louise Lang Lehrskov
louise.lang.lehrskov.01@regionh.dk

[1] The Centre of Inflammation and Metabolism (CIM) and the Centre for Physical Activity Research (CFAS), Rigshospitalet 7641, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark

The upstream stimuli for IL-6 secretion differ according to cell type. In immune cells, tumor necrosis factor-alpha (TNF-α) induces IL-6 secretion upon activation of the nuclear factor-κβ signaling pathway. Conversely, in skeletal muscle, IL-6 secretion is not induced by TNF-α-mediated nuclear factor-κβ activation, but is suggested to result from increased cytosolic Ca^{2+} and activation of P38 mitogen-activated protein kinase or calcineurin during skeletal muscle contraction [7]. Moreover, a recent study identified lactate production as a mediator of IL-6 release from muscle fibers [8].

Upon secretion, IL-6 mediates its biological effects via two distinct pathways, the classic signaling pathway and the trans-signaling pathway. The classic signaling occurs when IL-6 binds to its transmembrane IL-6 receptor (IL-6R) on target cells. The IL-6/IL-6R complex associates with the transmembrane signal-transducing glycoprotein 130 (gp130) and thereby activates downstream signaling cascades [4]. IL-6 can also signal via an alternative route called "trans-signaling" by binding to its soluble receptor [9, 10]. When IL-6 binds to the soluble IL-6 receptor (sIL-6R), a soluble complex is formed. This soluble complex then binds to gp130, and as gp130 is ubiquitously expressed on cells in the entire body, the IL-6/sIL-6 complex is able to signal in most tissues [11, 12]. The downstream signal transduction of IL-6 involves different intracellular pathways that include the JAK-STAT3, JAK-SHP-2-MAPK, and the PI3K pathway [11–14].

Taken together, IL-6 is not only secreted by a broad range of cells but can also target cells universally, and due to its various upstream and downstream signaling pathways, the final outcome of IL-6 signaling depends on the interplay of the type of target cell, its intracellular environment, and concomitant external stimuli of the cell [4]. Again, this highlights the tremendous pleotropic nature of IL-6. Therefore, it is not surprising that IL-6 is implicated in the regulation of the immune system (having both pro- and anti-inflammatory effects), bone metabolism, the nervous system, the hemopoietic system, the endocrine system, energy metabolism, glucose homeostasis, and lipid metabolism [4].

Interleukin-6 elevation during acute and chronic inflammation

Due to acute elevations of IL-6 in the initial phase of an infection or in response to noninfectious stimuli such as a burn or traumatic injuries, early studies identified IL-6 as a pro-inflammatory cytokine [15]. In these contexts, macrophages and monocytes secrete IL-6, leading to concentrations that are up to 1000 times higher than baseline circulating levels [16]. Increased concentrations of pro-inflammatory cytokines such as interleukin-1 (IL-1) and TNF-α precede and are the main inducers of the IL-6 elevation [17–20]. IL-6 then stimulates the secretion of various acute phase proteins, e.g., C-reactive protein (CRP) [21] that acts as warning signals, supporting the immune system in eliminating the source of stress from the system [22]. Thus, in the context of acute inflammation, elevation of IL-6 is a protective and beneficial response.

The role of IL-6 during chronic inflammation is still not well understood. Chronic low-grade inflammation is characterized by a two- to threefold elevation in systemic concentrations of cytokines (IL-1, TNF-α, and IL-6) and acute phase proteins, e.g., CRP [23, 24]. Chronic low-grade inflammation is found in states of the so-called metaflammation, observed in the metabolic syndrome, obesity, and type 2 diabetes mellitus (T2DM) [25]. A central source of cytokines in "metaflammation" is the adipose tissue, infiltrated by macrophages [5, 25, 26]. The inflamed adipose tissue is believed to arise due to hypertrophic adipocyte expansion that leads to compression of capillaries and tissue ischemia. This, in turn, leads to necrosis of the adipocytes and attraction of macrophages, which trigger the secretion of IL-6, TNF-α, IL-1β, and other pro-inflammatory cytokines [27]. While low-grade inflammatory factors such as TNF-α and IL-1β are implicated in insulin resistance and development of T2DM [28], the contributing role of IL-6 in metabolic disease is less established (reviewed in the subsequent sections).

Interleukin-6 elevation during exercise

Today, it is well known that during exercise muscle contractions lead to increased systemic concentrations of various peptides and cytokines, including IL-6, interleukin-1 receptor antagonist (IL-1ra), and interleukin-10 (IL-10) [29–31]. In 2003, it was proposed that a cytokine or a peptide produced, expressed, and released by muscle fibers in response to exercise, exerting autocrine, paracrine, or endocrine effects, should be named a "myokine" [32].

Thus, IL-6 was the first myokine to be discovered and has since been studied most extensively [33, 34]. IL-6 is the first detectable cytokine in the circulation [7] and it increases exponentially (up to 100-fold) [35–37], proportional to the duration of exercise and the amount of muscle mass engaged in the exercise [35]. Exercise-induced IL-6 occurs without a preceding increase in the pro-inflammatory cytokines TNF-a and IL-1 [38, 39] and initiates an anti-inflammatory response, as it inhibits the expression of TNF-α and IL-1 [20, 29, 40] and stimulates the production of the anti-inflammatory molecule IL-1ra [41], soluble TNF-α-receptors (sTNF-αR) [42], and IL-10 [43] among others.

The role of IL-6 in glucose homeostasis

The interest in IL-6 in energy metabolism arose from studies in IL-6-deficient mice showing that mice lacking IL-6 develop mature-onset obesity along with glucose intolerance [44, 45]. Today, it is well established that IL-6 regulates glucose

homeostasis; however, whether its role is beneficial or detrimental is debated [46].

The generally accepted view of IL-6 as a "bad guy" with regard to glucose homeostasis is primarily based on epidemiological studies showing a correlational relationship, in vitro cell culture studies of supraphysiological concentrations of IL-6, and some animal studies [47]. Epidemiological studies have revealed that IL-6 is implicated in the chronic inflammation that accompanies conditions such as obesity and T2DM [47].

In support of this idea, infusions of IL-6 have been shown to impair insulin action in mice [48], whereas blocking of IL-6 signaling improves hepatic insulin sensitivity [49]. These findings suggest that IL-6 may be involved in hepatic insulin resistance, which may derive from increased phosphorylation of SOCS3 that binds insulin receptor substrates (IRS) and targets them for proteasomal degradation, thus impeding insulin-mediated glucose uptake [50]. However, the negative effects of IL-6 in the liver appear to arise only when IL-6 is secreted from the adipose tissue [51].

In contrast to the view of IL-6 as a "bad guy" in the regulation of glucose homeostasis, a growing body of evidence indicates that chronically elevated IL-6 is beneficial, as increased levels might serve as an adaptive mechanism aiming at improving glycemic control. In line with this, a study by Ellingsgaard et al. showed that IL-6 knockout mice on a high-fat diet were unable to expand the pancreatic alpha-cell mass, resulting in reduced glucose-stimulated insulin secretion (a beta-cell defect). In this context, increased IL-6 was seen as an adaptive response, necessary to maintain proper insulin secretion and glycemic control in response to a high-fat diet [52]. Subsequent studies by the same group demonstrated that IL-6 mediates cross-talk between insulin-sensitive tissues and pancreatic beta-cells via the incretin hormone glucagon-like peptide-1 (GLP-1). More specifically, IL-6 was shown to promote enhancement of GLP-1 production and consequently increased secretion of insulin [53]. Another study confirmed that IL-6 regulates the incretin axis, as glucose regulatory action of the other incretin hormone glucose insulinotropic polypeptide (GIP) was found to be mediated via IL-6 [54].

the Brüning group recently identified IL-6 as an important determinant of the alternative activation of macrophages, as IL-6 counterbalance a shift of macrophage populations toward a pro-inflammatory phenotype, indicating a role of IL-6 in limiting systemic inflammation [55]. Later, the same group showed that IL-6, trans-signaling in the central nervous system (CNS), suppresses feeding and improves glycemic control, an effect that seems to be enhanced in obese mice [56]. In addition, Mauer et al. showed that IL-6 signaling limits systemic inflammation and improves glycemic control in macrophages and hepatocytes of lean and obese mice [55, 57]. Correspondingly, another group proposed that increased IL-6 mRNA in insulin-resistant tissues may be an attempt to overcome the metabolic dysfunction [58].

Taken together, elevation of IL-6 during low-grade inflammation may serve as an adaptive mechanism in an attempt to increase insulin production and improve glucose homeostasis at least in mouse models. However, there seem to be differences between the actions of IL-6 in mice and in humans, and some of the effects of IL-6 may be species-specific [59]. In support of this, mouse IL-6 is only 42% identical to the human IL-6 molecule [60, 61].

A beneficial role of acutely elevated IL-6 in glucose homeostasis is suggested from exercise studies, where an acute bout of exercise with elevations of plasma IL-6 increases glucose uptake in the periphery [62]. It would indeed be a counterintuitive physiological response to release a factor that promotes insulin resistance, in a condition where increased insulin sensitivity is needed. In cell culture studies, increased glucose uptake was accompanied by translocation of the glucose transporter GLUT4 from intracellular compartments to the plasma membrane in skeletal myotubes [63]. Moreover, IL-6-induced IL-1ra during exercise is speculated to result in limited IL-1-induced pancreas damage and thus improved insulin secretion [62, 64]. However, whether IL-6 plays a role for the adaptations in glucose homeostasis occurring with exercise in humans remains to be clarified.

In humans, a huge increase in circulating IL-6 (by means of an infusion) induces fever, release of catecholamines, and elevated plasma glucose levels [65, 66]. In contrast, a modest elevation of plasma IL-6, comparable to the IL-6 elevation induced by exercise, seems to induce an anti-inflammatory and mostly beneficial effect in the maintenance of glucose homeostasis in humans. Despite the overall positive effects of short-term IL-6 exposure, the effects seem to be context dependent [43, 67–69]. An infusion of recombinant IL-6 in physiological concentrations improves insulin sensitivity during a hyperinsulinemic, euglycaemic clamp in healthy individuals [63], but not in patients with T2DM [70]. In support of this context dependency, an infusion of IL-6 was found to increase endogenous hepatic glucose production (revealing a direct muscle-liver cross-talk) [69]; however, this was observed exclusively during exercise, whereas no effect was found during resting conditions [43, 67, 68].

In line with the above-described beneficial effects of an acute increase in IL-6, we recently showed that infusing IL-6 prior to a meal improves postprandial glucose homeostasis in humans (Fig. 1). More specifically, we came across a previously unidentified role of acutely increased IL-6 (by an infusion or an acute bout of exercise) in delaying the rate of gastric emptying. Our studies demonstrated that an infusion of IL-6 delay gastric emptying rate, leading to a reduction in postprandial glucose. Moreover, independent of gastric emptying rate, IL-6 reduces postprandial insulin secretion. The effects of IL-6 on gastric emptying and insulin secretion were maintained in patients with T2DM [59].

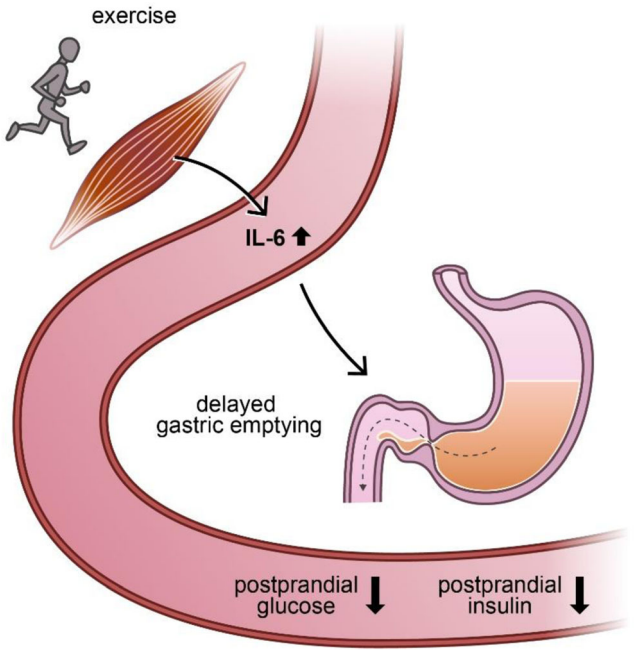

Fig. 1 In a series of human studies performed at the Centre for Physical Activity Research, an acute increase in IL-6 (by an infusion or an acute bout of exercise) delayed gastric emptying rate. Following an IL-6 infusion, the deceleration in gastric emptying rate reduced postprandial glucose. In addition, IL-6 reduced postprandial insulin. Thus, an acute increase in IL-6 delays gastric emptying with direct effects on glucose homeostasis in humans. Adapted with permission from Lang Lehrskov et al. [59]

In conclusion, IL-6 regulation of glucose homeostasis is complex and still not fully understood. The conflicting observations regarding the metabolic role of IL-6 stimulate the ongoing debate as to whether IL-6 is good or bad in the context of low-grade inflammation in humans.

Given the various glucose regulatory effects of IL-6, we need to be aware of the metabolic consequences of IL-6 blockade in auto-immune/inflammatory disease (reviewed in the subsequent sections).

Furthermore, it is tempting to pose the question whether the effects of acute IL-6 administration might be exploited for therapy to improve glycemia. To be able to answer this, further studies are needed to address how IL-6 exerts its actions, and whether the potential beneficial effects of IL-6 are preserved in different metabolic states (obesity, metabolic syndrome, and type 2 diabetes).

The role of IL-6 in lipid metabolism

IL-6 is suggested to participate in mediating the obesity-associated insulin resistance preceding T2DM [71]. The rationale for this is based on studies showing an association between elevated circulating levels of IL-6 due to obesity and insulin resistance in liver and adipose tissue [71].

Conversely, mounting evidence has consolidated a central role of IL-6 in the regulation of lipid metabolism. IL-6 has been identified as a lipolytic factor from studies in mice, where IL-6 knockout mice developed mature-onset obesity that was partly reversed after repetitive infusions of IL-6 [44]. A subsequent study showed that chronic administration of IL-6 results in reductions in rodent mesenteric and retroperitoneal fat depots [44]. Transgenic mice overexpressing IL-6 have been shown to stay lean and be protected from the adverse effects of a high-fat diet [72]. Based on these findings, an anti-obesity effect of IL-6 has been suggested [73]. Furthermore, we know from studies in humans that a single infusion of IL-6 stimulates lipolysis and β oxidation at the whole-body level [74], both when administered at high and low doses [75]. The lack of a concomitant increase in plasma adrenaline or insulin indicates that the effect is driven by IL-6 per se. Another study demonstrated an increased glycerol release from subcutaneous adipose tissue in response to an acute IL-6 infusion [76]. Of note, patients with Castleman's disease (abnormal production of IL-6 by germinal center B cells) are characterized by hypolipidemia [77]. These findings of IL-6 as a critical regulator of lipolysis and β oxidation have been confirmed by multiple in vitro studies demonstrating that IL-6 treatment increases lipolysis and β oxidation both in myotubes and adipocytes [63, 74, 78, 79]. Lipolysis has been shown to be stimulated by IL-6 in several adipose tissue depots, including human subcutaneous and visceral depots [80]; however, the specific molecular mechanism conveying lipolysis in adipose tissue remains unknown, but may involve activation of AMP-activated kinase (AMPK) [63, 79, 81]. In contrast, it is well known that IL-6 induces β oxidation via AMPK [7, 63, 79, 81]. AMPK phosphorylates and inactivates acetyl CoA carboxylase β (ACCβ), which decreases malonyl-CoA content and thus relieves its allosteric inhibition of carnitine-palmitoyl transferase 1 (CPT-1) [82, 83]. CPT-1 catalyzes the formation of carnitine-acyl and transports into the mitochondrion where β oxidation takes place [84].

Other roles for IL-6 in lipid metabolism include IL-6-stimulated leptin secretion from human omental and subcutaneous adipose tissues as demonstrated by Trujillo et al. [80], which may affect appetite and caloric intake. They also found that IL-6 decreased lipoprotein lipase (LPL) activity by 56% in omental and by 68% in subcutaneous adipose tissue. These findings indicate that IL-6 may act to diminish lipid uptake and deposition in adipose tissue and suggest the concept of IL-6 as an "adipostat" which controls adipocyte size [80].

Overall, solid evidence exists that IL-6 plays an essential physiological role in the regulation of adipose tissue and lipid metabolism. As such, the notion of IL-6 as an anti-obesity agent should be "weighed" against its

importance as a causal driver of the development and progression of obesity-associated diseases such as T2DM.

The implication of IL-6 receptor blockade in inflammatory diseases

IL-6 is the major mediator of inflammatory joint destruction in rheumatoid arthritis (RA) [85] and thus, in 2010, the IL-6 receptor antibody, tocilizumab, the only available medical treatment targeting IL-6 signaling, was approved for the treatment of moderate to severe rheumatoid arthritis [86]. Today, tocilizumab is also approved for the treatment of other inflammation-related diseases such as Castleman's disease and systemic juvenile idiopathic arthritis [87]. Moreover, it is debated whether tocilizumab can be used also in the treatment of other diseases with elevated IL-6 levels (other autoimmune diseases, malignant diseases, cardiovascular disease, and T2DM) [86]. Even though the potential of targeting inflammation by tocilizumab in the treatment of T2DM is intriguing, the recognition of IL-6 as a pleiotropic factor with important effects on metabolism is paramount and the effects of IL-6 blockade on metabolism need first to be clarified.

The implication of IL-6 receptor blockade on glucose homeostasis

Given that IL-6 is speculated to be a co-inducer of the development of insulin resistance associated with obesity, the idea of blocking IL-6 in order to prevent and treat hyperglycemia has gained attention [88, 89]. Several studies point toward a beneficial effect of IL-6 receptor blockade on glycemic control in patients treated with tocilizumab with and without T2DM [90–93]. In patients with RA, hba1c levels were decreased after the initiation of tocilizumab treatment [94], and a review concluded that tocilizumab improves insulin sensitivity in inflammatory arthritis [92].

However, as discussed above, the role of IL-6 in the regulation of insulin sensitivity and overall glucose homeostasis is rather complex. Thus, even though treatment with IL-6 blockade to prevent or treat T2DM may seem appealing, it still remains unexplored and further research is needed.

Along this line, anti-inflammatory treatment with IL-1 blockade and other anti-inflammatory agents have recently been suggested as potential candidates to treat or prevent diabetes [89, 95].

The implication of IL-6 receptor blockade on lipid metabolism

Based on the solid evidence of IL-6 being a lipolytic factor, it has been speculated whether IL-6 receptor blockade in the treatment of inflammatory disorders may lead to the unwanted side effects of obesity, i.e., insulin resistance/T2DM, and cardiometabolic morbidity and mortality, thus opposing its potential as a treatment for immunometabolic diseases.

Addressing this concern, studies in humans receiving tocilizumab have consistently shown increased systemic levels of cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides, which are well-known adverse effects in patients receiving tocilizumab, as reviewed by Choy et al. [96]. Recently, our research group has performed a randomized placebo-controlled trial including abdominally obese and physically inactive, but otherwise healthy, people for a 12-week exercise intervention with concomitant blockade of IL-6 signaling by tocilizumab [97]. The study demonstrated that blocking IL-6 signaling during aerobic bike training completely abolishes the exercise-induced reduction of visceral adipose tissue (Fig. 2). This finding reveals that IL-6 is required to obtain the adipose tissue-reducing effects of exercise and consolidates the role of IL-6 in the regulation of lipid metabolism. Moreover, LDL and total cholesterol were increased by tocilizumab, and this increase was not reversed by exercise.

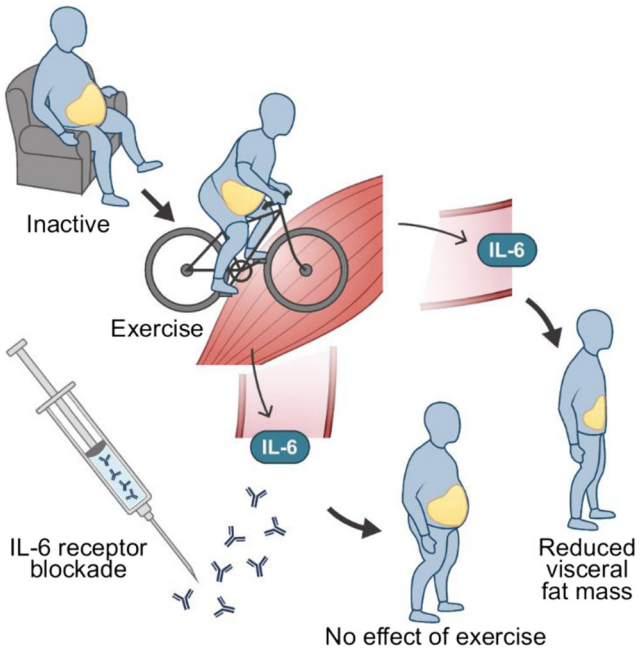

Fig. 2 A recent randomized placebo-controlled trial including abdominally obese, inactive participants, performed at the Centre for Physical Activity Research, demonstrated that IL-6 receptor blockade abolishes the fat-reducing effects of aerobic bike exercise. Thus, IL-6 signaling is a requirement for reduction in visceral adipose tissue following exercise. Adapted with permission from Wedell-Neergaard et al. [97]

Clinical considerations of IL-6 receptor blockade in immunometabolic diseases

Several studies have confirmed the safety and efficacy of tocilizumab in reducing inflammation in patients with pro-inflammatory diseases [98, 99] and have sparked an interest to expand the application of tocilizumab for the treatment of immunometabolic diseases. To this end, emerging evidence, as reviewed above, suggests that blocking IL-6 signaling may improve glucose homeostasis in a context where IL-6 is chronically elevated. However, caution should be taken as the role of IL-6 in glucose homeostasis is complex and context-dependent as described above. In contrast to the potentially beneficial role of IL-6 receptor blockade on glucose homeostasis, IL-6 receptor blockade leads to weight gain and hyperlipidemia, which may oppose the idea of using IL-6 receptor blockade to treat metabolic disease. Interestingly, the adverse effects on lipid metabolism may not necessarily translate into an increased cardiometabolic risk, as implied by follow-up studies of patients treated with tocilizumab [100]. Therefore, the long-term importance of the beneficial and adverse metabolic consequences of IL-6 receptor antagonism needs to be further addressed to fully grasp the clinical potential of this drug in the treatment of metabolic diseases.

Conclusion

In conclusion, the pleotropic molecule IL-6 has both pro- and anti-inflammatory characteristics and the outcome of IL-6 signaling depends on the context. During acute inflammation, IL-6 is a key player in orchestrating the acute immune response to control an infectious stimulus, which involves both IL-6-mediated induction of anti-inflammatory cytokines (IL-1ra, IL-8, IL-10, etc.) and acute phase reactants, including CRP. Chronic low-grade inflammation is a defining feature of metabolic diseases, where circulating levels of IL-6, TNF-α, IL-1β, and other cytokines are increased. Recently, chronic low-grade inflammation has been recognized as a driver of adverse metabolic effects. Therefore, it is intriguing to suggest the low-grade inflammatory cytokines as targets for antibody-based treatment strategies for metabolic diseases. Yet, while research shows promising results of antibodies directed at IL-1β in the treatment of metabolic disease, the potential of anti-IL-6-based therapies may be more challenging due to the paramount role of this myokine in metabolism: IL-6 is an important regulator of glucose metabolism; however, its role is complex and context- and species-dependent, so that in some situations, it improves while in other, it aggravates insulin sensitivity and glucose homeostasis. In regard to lipid metabolism, solid evidence has identified IL-6 as a lipolytic factor. IL-6 stimulates lipolysis and β oxidation, increases leptin, and reduces lipoprotein lipase, which has led to the suggestion that IL-6 is an "adipostat" that attempts to control and prevent adipocyte hypertrophy. Overall, this complex role of IL-6 in glucose homeostasis and the anti-obesity effect of IL-6 warrant further research and apparently "weigh" against the potential of treating metabolic diseases with antibody-based therapies that neutralize IL-6.

Acknowledgments We are grateful to Helga Ellingsgaard for providing us the opportunity to write this review. The Centre for Physical Activity Research (CFAS) is supported by a grant from TrygFonden.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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