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REVIEW

Anti-inflammatory action and effects on carbohydrate and lipid metabolism: an understudied role of interleukin-6

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ABSTRACT. Interleukin-6 (IL-6) is a cytokine with pleiotropic effects that plays a significant role in the transition from the innate immune response to adaptive response. IL-6 is of interest due to its proinflammatory action, however, it also exhibits anti-inflammatory effects, supporting metabolism and suppressing associated diseases, such as obesity, diabetes mellitus and metabolic syndrome. The IL-6 receptor (IL-6R) is a type I transmembrane glycoprotein in the plasma membrane of only some cell types, such as macrophages, neutrophils, hepatocytes, and T cells. The function of IL-6R requires another transmembrane glycoprotein of 130 kDa (gp130) which, in contrast to IL-6R, is expressed in many cell types. In addition, a soluble form of the IL-6 receptor (sIL-6R) also plays a role in the function of IL-6. These receptors, gp130 and sIL-6R, are involved in the *trans* pathway of IL-6 signalling, the activation of which is associated with high IL-6 concentrations, promoting proinflammatory processes that are well known. In contrast, the physiological effects of IL-6 associated with increased insulin secretion, fatty acid oxidation and decreased adipose tissue, which occur due to activation of the IL-6 anti-inflammatory signalling pathway, have been poorly explored. Some studies using IL-6 knockout models suggest that some of the anti-inflammatory effects of IL-6 may be stimulated by low concentrations of IL-6, and are essential to suppressing metabolic alterations. This review seeks to highlight the importance of the anti-inflammatory role of IL-6 in metabolic diseases.

Key words: interleukin-6, anti-inflammatory action, IL-6 receptor, lipid metabolism, carbohydrate metabolism

Interleukin 6 (IL-6) is a protein of the IL-6 type cytokine family [1,2]. It consists of 212 amino acid residues, including a 28-residue signal peptide, forming a bundle-shaped structure of four α-helices of 21 to 28 kDa [1,3]. IL-6 was discovered and identified when the cDNA encoding for B-cell stimulatory factor 2 (BSF-2) was cloned in 1986. It was then named BSF-2, as well as hepatocyte-stimulating factor, hybridoma-plasmacytoma growth factor, interferon β2, and the 26-kDa protein [4,5]. IL-6 is associated with the transition from an innate immune response towards an adaptive response and has been proposed as a modulator of the immune response [4,6].

IL-6 is associated with pro-inflammatory processes. The overproduction of this cytokine leads to alterations in tissues, favouring the development of multiple chronic inflammatory diseases that include rheumatoid arthritis [7], Castleman's disease [8], polymyalgia rheumatica [9], giant cell arteritis [10], and colon cancer [11]. In contrast, IL-6 also exhibits anti-inflammatory effects and participates in the regulation of carbohydrate and lipid metabolism [12]. In this review, the results of recent investigations on this cytokine are presented and the main molecular mechanisms of action of IL-6 are discussed.

REGULATION OF IL-6 GENE EXPRESSION

IL-6 acts before an event emerges. Many cell types, including stromal and immune cells, produce IL-6 in response to exogenous stimuli, including bacterial, viral or fungal antigens that activate pathogen recognition receptors (PRRs), such as Toll-like receptors [13]. The concentration of circulating IL-6 in the normal human adult bloodstream fluctuates between 1 and 5 pg/mL, however, this concentration dramatically increases under inflammatory conditions [14]. IL-6 participates in tissue damage through damage-associated molecular patterns (DAMPs), involving molecules synthesized from mitochondrial DNA, high mobility group proteins (HMGB1) or s100 proteins, which are released by damaged or dead cells during non-infectious processes, triggering inflammatory events [15].

The regulatory factors of IL-6 gene expression have been described to several levels. In the upstream promotor region of the IL-6 gene, there are different DNA *cis* elements that interact with several proteins or *trans* elements [16]. The transcription factor NF-κB is the main regulator of IL-6 expression. NF-κB binds to specific sequences located in the -75 to -64 upstream region

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of the IL-6 promoter [17, 18]. The binding and activation of NF-κB occurs in response to stimuli from bacterial or viral infections and, consequently, by TNFα and IL-1β [19].
Another site within the IL-6 promoter is the cAMP response element (CRE) [20], which allows for binding of CREB transcription factor, activated by β-adrenergic agonists which are mediated by G protein-coupled receptors (GPCRs). Norepinephrine can induce IL-6 secretion in gastric epithelial cells [21]. Synthetic agonists, such as isoproterenol, also induce IL-6 secretion in Balb/c mouse cardiac fibroblasts [22]. In this region where the CRE is located, there is a binding site for another transcription factor, C/EBPβ (also called NF-IL6) [23]. All these sequences are together located between -164 and -145 bp [24], and present a high degree of homology between mice and humans [25].
Other elements that regulate the expression of IL-6 have also been reported, such as an activation protein 1 (AP-1) binding motif [26], also known as a TPA response element, located at -283 to -277 bp [19]. When AP-1 binds to its DNA consensus binding site, it exerts a significant effect on IL-6 expression [27].
Steroid hormones are also capable of exerting effects on the expression of IL-6. When a steroid binds to its receptor, it migrates to the nucleus and binds to a DNA consensus sequence known as a steroid response element, which is present in the promoter region of the IL-6 gene. In humans, a pair of glucocorticoid response elements (GREs) are located at positions -557 to -552 and -446 to -441 bp [28]. When the alpha subunit of glucocorticoid receptor binds to GREs, it acts as a negative regulator of proinflammatory cytokine expression, in addition to binding to transcription factors, such as NF-κB or AP-1 [29, 30]. Therefore, glucocorticoids may play a role in the anti-inflammatory action of IL-6.
On the other hand, oestrogens can negatively regulate the expression of IL-6 through the interaction of oestrogen receptor with the DNA-binding domains of transcription factors, such as NF-κB or NF-IL6 [31]. This regulation of IL-6 is also mediated by androgens [32].

IL-6 RECEPTOR

The IL-6 receptor (IL-6R) is an 80-kDa type I transmembrane glycoprotein. The α subunit of the receptor is also known as CD126 [33, 34]. This protein is expressed on the plasma membrane of a very limited number of cell types, including macrophages, neutrophils, hepatocytes, and some types of T cells [6, 33, 35]. A particular characteristic of IL-6R is that it requires another 130-kDa transmembrane glycoprotein, the β subunit of the receptor, called gp130 (or CD130), which is responsible for initiation of signal transduction within the cell [3, 33, 34, 35]. It is important to note that IL-6R is not capable of activating signalling if gp130 is not present.
Contrary to the expression of IL-6R, restricted to very few cell types, gp130 is expressed in practically all cell types present in the body [1, 35]. Functional and structural studies suggest that the formation of a hexameric complex formed by two molecules of IL-6, IL-6R and gp130 (IL-62/IL-6R2/gp1302) is necessary [36, 37]. Another model proposed involves the formation of a tetrameric complex (IL-61/IL-6R1/gp1302) [38].
These models indicate that the type of complex formed depends on the concentration of circulating IL-6, since high concentrations of IL-6 appear to favour the formation of the hexameric complex, while low concentrations favour formation of the tetrameric complex (*figure 1*) [39-41]. The study of these complexes between IL-6 and its receptors is of interest because they are possibly involved in activating specific signals responsible for the attributed pleiotropic action of IL-6. Moreover, IL-6 signalling, involving gp130, is implicated in the regulation of insulin sensitivity, leading to disorders such as obesity and diabetes [42].
The canonical signalling pathway of IL-6 is activated when the cytokine binds to its receptor in the cell plasma membrane (mbIL-6R) [3, 1, 34], however, another mechanism called "*trans*-signalling" has been described, in which a soluble form of IL-6R (sIL-6R) also plays a role [1, 3, 6]. There are two mechanisms that are believed to be involved in the formation of sIL-6R. The first is via metalloproteases of the ADAM family (particularly ADAM10 and ADAM17), which are responsible for "cutting" the receptor in the membrane of cells that express and release it. The second mechanism involves alternative splicing of the IL-6R, causing a change in the reading frame which results in a protein without a transmembrane and cytosolic domain, but with the ability to interact with its ligand and form the IL-6/sIL-6R complex. Interestingly, the IL-6/sIL-6R complex can freely circulate and bind to gp130 of cells that do not express IL-6R on their surface, and thus respond to IL-6 stimulation [6, 33, 35].
Also, a soluble form of gp130 (sgp130) has been detected in human blood [43]. This soluble form is produced mainly via alternative splicing [44] and can interact with the IL-6/sIL-6R complex, acting as a specific inhibitor of *trans*-signalling, while having no significant effect on the classic IL-6/sIL-6R signalling complex [45].

IL-6 INTRACELLULAR SIGNALLING

The binding of IL-6 to its receptor activates different signal transduction pathways, and the JAK/STAT pathway is the main and best studied. The group of tyrosine kinases, known as janus kinases (JAKs), participate in this pathway and phosphorylate tyrosine residues in the intracellular domain of gp130. Another group of proteins, known as signal transducers and activators of transcription (STATs), mainly STAT1 and STAT3, are recruited to gp130 and interact with it through specific phosphorylated tyrosine residues [46]. STATs are then also phosphorylated at their specific tyrosine residues, allowing homodimers or heterodimers to form which are translocated to the nucleus, acting as transcription factors that regulate the expression of different target genes, many of which are involved in the immune response [3, 47]. In the liver, this IL-6 signalling pathway promotes the synthesis of a group of proteins known as "acute-phase proteins", including C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin, and haptoglobin anti-chymotrypsin α [48].

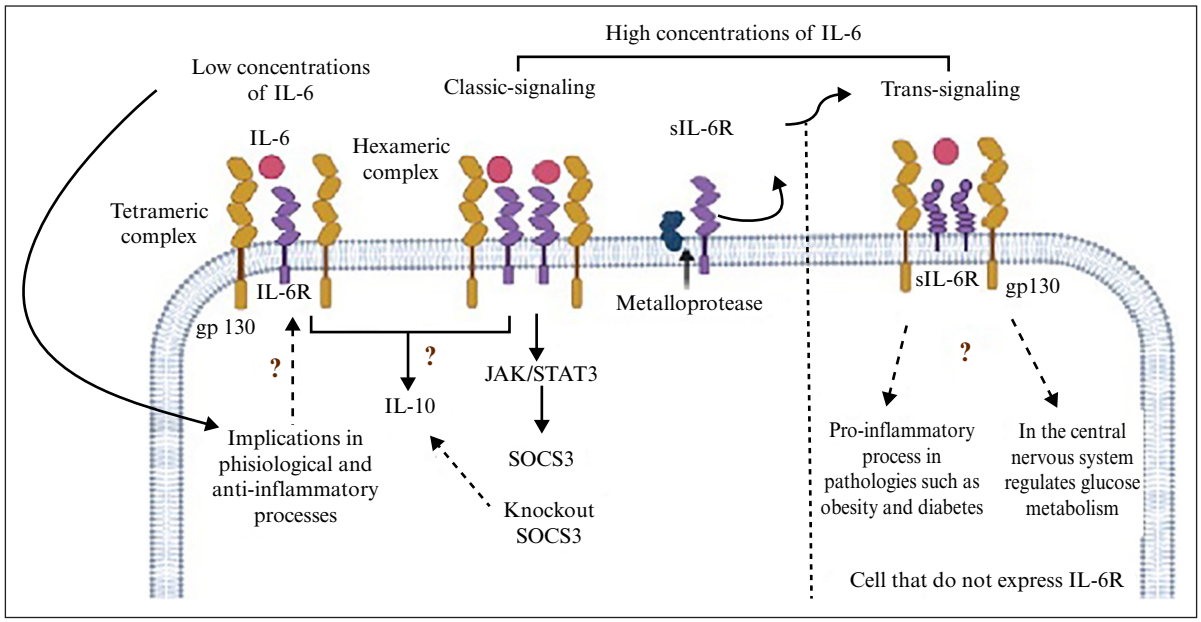

Figure 1
Schematic diagram showing IL-6 receptor complexes and their signalling. At high concentrations of IL-6, the hexameric complex (IL-62/IL-6R2/gp1302) of IL-6 forms and activates the trans pathway or the canonical pathway involved in the inflammatory process, although the trans pathway may positively regulate glucose metabolism. However, in the anti-inflammatory pathway, the complex formed and the associated signalling pathway are unclear. Interestingly, upon activation of the IL-6 receptor in SOCS3 knockout cells, the expression of IL-10 (an anti-inflammatory cytokine) is increased, which would indicate that IL-6 could play an anti-inflammatory role in the absence of SOCS3, however, evidence for this is lacking.

A particular aspect of STAT signalling is that it exhibits negative feedback, regulating the transcription of proteins that act as inhibitors of the pathway at different levels. The main proteins are suppressors of cytokine-mediated signalling (SOCS), for example, SOCS1 that binds to phosphorylated tyrosine residues of JAKs to inhibit their kinase activity [49] or SOCS3 that binds to phosphorylated tyrosine residues on gp130 [50]. SOCS3 knockout macrophage cell lines [51] and hepatocytes differ in the duration of signalling after stimulation with IL-6, which does not affect the initiation of signalling but results in prolonged activation of STAT1 and STAT3 [52].

The proinflammatory effect of IL-6 appears to be strongly related, most of the time, to *trans*-signalling [53]. sIL-6R allows cells to react to signals induced by pathogens or by some type of damage. At high concentrations of IL-6, sIL-6R binds to IL-6 to activate *trans*-signalling [54]. Therefore, it may be deduced that the activation of signalling will depend on the concentration of IL-6. Few studies have addressed anti-inflammatory signalling of IL-6, therefore, research should focus on studies to identify signalling molecules downstream of the activated pathway (canonical or *trans*).

ANTI-INFLAMMATORY EFFECT OF IL-6 ON CELLS OF THE IMMUNE SYSTEM

In one of the first studies in which the anti-inflammatory effect of IL-6 was demonstrated, IL-$6^{+/+}$ and IL-$6^{-/-}$ mice were subjected to systemic and local endotoxemia in the lungs. In IL-$6^{-/-}$ mice, the levels of proinflammatory cytokines (TNFα, MIP-2, IFNγ) were significantly higher than those in IL-$6^{+/+}$ mice. Also, administration of IL-6 to IL-$6^{-/-}$ mice further decreased the levels of pro-inflammatory cytokines. Therefore, endogenous IL-6 plays an anti-inflammatory role by controlling the levels of proinflammatory cytokines without the involvement of anti-inflammatory cytokines, such as IL-10 [55].

In macrophages, IL-6 induces an anti-inflammatory effect in the absence of SOCS3. In macrophages from SOCS3 knockout mice exposed to LPS, the production of TNFα and IL-12 is suppressed by IL-6 and IL-10. Therefore, the absence of SOCS3 promotes the production of TNFα and IL-12. IL-6 generates an anti-inflammatory response, similar to that of IL-10. Both IL-6 and IL-10 act through STAT3, but SOCS3 selectively inhibits STAT3 activity only when it is induced by IL-6 and not by IL-10 [51].

IL-6 acts synergistically with TGF-β to induce IL-10 expression in Th-17 cells [56]. Naïve CD4+ cells exposed to IL-6 generate a phenotypic change similar to that of type 1 regulatory T cells (Tr1), and are capable of secreting IL-10, in the absence of TGF-β. Based on an *in vivo* model of multiorgan inflammation, blocking IL-6-mediated signalling resulted in decreased production of IL-10 in T cells and increased inflammation in the lungs and intestine [57]. In contrast to pro-inflammatory studies of IL-6, anti-inflammatory effects have been poorly studied, and there is a wide scope for further studies to clarify the signalling pathways involved and effects on cells.

ANTI-INFLAMMATORY EFFECT OF IL-6 IN MUSCLE TISSUE

Skeletal muscle is the most abundant tissue in the human body and plays a relevant role in the secretion

of IL-6, induced by physical activity and exercise. IL-6 is the first cytokine to appear in the serum of subjects subjected to high-intensity exercise, and its concentration can increase up to 100 times and decrease after such activity [58]. Although it was postulated that this increase in IL-6 was a consequence of the damage caused to muscle fibres, other major proinflammatory markers, such as TNFα and IL-1β, do not increase. Therefore, cytokine secretion during exercise is different to that occurring during an infection [59].
During exercise, an increase in circulating IL-6 leads to a rise in IL-10 concentration and the IL-1 receptor antagonist (IL-1Ra) [60], as well as release of the soluble TNFα receptor, which has an inhibitory effect on TNFα [61]. Administration of recombinant human IL-6 (rhIL-6) mimics the effect of exercise, promoting IL-6 secretion and inhibiting the increase in plasma TNFα production induced by endotoxemia in humans [62].

ANTI-INFLAMMATORY EFFECT OF IL-6 IN THE LIVER

In hepatocytes, IL-6 can induce the production of some acute-phase proteins with anti-inflammatory activity, including IL-1Ra [63] or CRP. The latter also slightly increases in plasma after exercise, inducing anti-inflammatory cytokine secretion in circulating monocytes and suppressing pro-inflammatory cytokine synthesis in tissue-resident macrophages [64].

ANTI-INFLAMMATORY EFFECT OF IL-6 IN ADIPOSE TISSUE

During obesity, a low-grade inflammatory disease develops that is mediated by adipose tissue macrophages, which can be classified according to their phenotype, as M1 or proinflammatory and M2 or anti-inflammatory. Adipose tissue macrophages from lean subjects express genes associated with the M2 phenotype, while those from overweight or obese subjects predominately express genes associated with the M1 phenotype. This latter phenotype contributes to characteristic inflammation of adipose tissue, through the release of many proinflammatory cytokines (TNFα, IL-1β, IL-6) and chemokines that attract more cells, such as monocytes and neutrophils, to adipose tissue [65].
In experiments carried out in myeloid cells lacking the IL-6R α subunit, a pattern of gene expression was observed similar to that of macrophages with the M1 phenotype, *in vitro* and *in vivo*, and treatment with recombinant IL-6 contributed to the acquisition of an M2 phenotype, mediated also by IL-4, another anti-inflammatory cytokine. In IL-6Rα knockout mice fed with a high-fat diet, many macrophages acquired an M1 phenotype, inducing inflammation in adipose tissue, while the number of M2 macrophages was greatly reduced, suggesting that IL-6 has an important effect on the acquisition of a proinflammatory or anti-inflammatory phenotype (*figure 2*) [66].

EFFECT OF IL-6 ON LIPID METABOLISM

IL-6 also appears to play a role in lipid metabolism. Wallenius *et al.* showed that IL-6 knockout mice develop a very advanced obesity phenotype and IL-6 administration decreases adipose tissue [67]. Preadipocytes obtained from the adipose tissue of obese patients treated with IL-6 showed decreased expression of PPARγ and C/EBPα, with a lower adipogenic capacity [68]. In human adipocytes, IL-6 administration regulates lipid metabolism, increasing lipolysis in the absence of insulin, and increases leptin expression [69]. In lean and obese men, anti-IL-6 therapy impaired fat mobilization, which might contribute to an increase in adipose tissue mass and, thus, affect the health of individuals [70].
Peterson *et al.* observed that the administration of IL-6 in older adults produces an increase in the metabolism

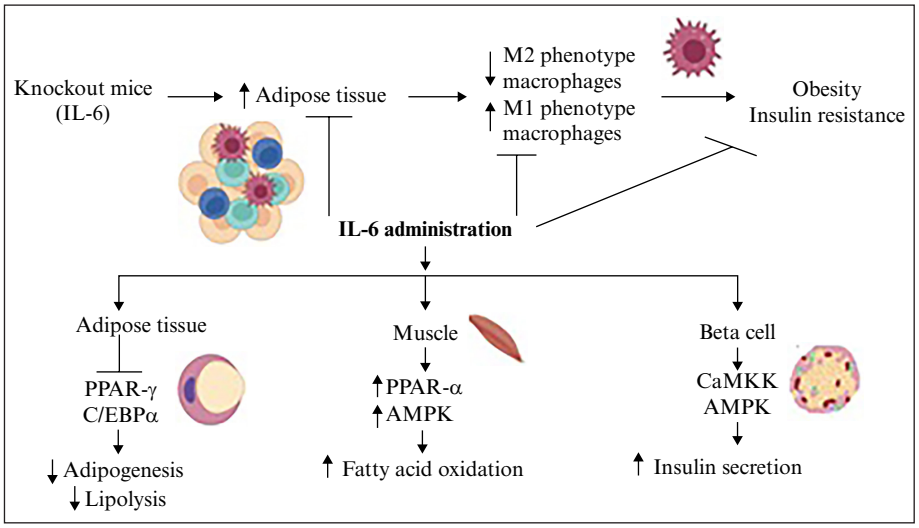

Figure 2
Anti-inflamatory and metabolic effects of IL-6. IL-6 knockout mice exhibit increased adipose tissue, M1 macrophages, inflammation, obesity, and insulin resistance. However, the administration of IL-6 induces an anti-inflammatory effect associated with an increase in M2 macrophages. IL-6 may inhibit adipogenesis and suppress the develomment of obesity, and in muscle, may increase fatty acid oxidation by regulating PPAR and AMPK. AMPK may also be modulated by IL-6 in the pancreas, improving insulin secretion.

of fatty acids without affecting insulin sensitivity. However, in the model of 3T3-L1 adipocytes treated with IL-6, an increase in lipolysis was observed through the quantification of glycerol released in the medium [71]. IL-6 also exerts effects on transcription factors that regulate lipid metabolism, such as PPARα, a nuclear receptor. By binding to saturated or unsaturated fatty acids, PPARα promotes the expression of enzymes involved in fatty acid oxidation, such as SREBP-1c, which is responsible for regulating the expression of lipogenic enzymes, favouring lipid synthesis. In Hep3B cells treated for 24 hours with IL-6, there was a significant increase in PPARα mRNA and a decrease in SREBP-1c. This same result was observed in mice after administration of IL-6 [72]. On the other hand, in humanized rodent liver models, activation of IL-6R and gp130 decreased lipid accumulation in hepatocytes, and independent activation of gp130 was sufficient to prevent the development of steatosis. In addition, Kupffer cells play an important role in the production of IL-6 and activation of the signalling pathway controlling lipid droplet accumulation in hepatocytes [73]. Therefore, IL-6, by regulating PPARs, has an important role in the regulation of lipid metabolism, however, it is important to clarify the pathways involved.

EFFECT OF IL-6 ON CARBOHYDRATE METABOLISM

Regarding the effects of IL-6 on the metabolism of carbohydrates, results are contradictory because IL-6 generates insulin resistance in both 3T3-L1 adipocytes *in vitro* [74] and experimental mouse models [75]. In contrast, the induction of IL-6 expression in human myotubes *in vitro* does not inhibit the effect of insulin or glycogen synthesis [76]. Moreover, acute administration of rhIL-6 to healthy subjects does not alter glucose internalization into adipose tissue or its endogenous generation [77]. In patients with type 2 diabetes, who received rhIL-6, plasmatic insulin levels decreased, suggesting that the administration of IL-6 improves sensitivity to insulin [71]. In IL-6 knockout mouse, insulin resistance and mature-onset obesity was observed, that was partly reversed after IL-6 administration, and it was concluded from this study that centrally acting IL-6 exerts anti-obesity effects in rodents [67]. In β-cells, the secretion of insulin was increased at IL-6 concentrations of 25 to 100 pg, after 20 minutes and 24 hours of treatment. In pancreatic islets isolated from C57BL/6J mice, an increase in insulin was observed after a two-hour incubation at a concentration of 100 to 1000 pg of IL-6. In addition, IL-6 is reported to induce insulin secretion through calmodulin-dependent protein kinase kinase (CaMKK) and subsequent AMPK activation [78].
Studies indicate that IL-6 *trans*-signalling is involved in signalling of the central nervous system in obese mice, exerting beneficial effects on glucose metabolism even under conditions of leptin resistance [79]. These contradictory data, regarding the fact that this pathway is involved in proinflammatory processes in obesity and may enhance metabolism at the level of the central nervous system, illustrate the complexity of IL-6 in relation to its pleiotropic action on different cell types.

In mice with a low and high-fat diet, IL-6 decreased blood glucose and mRNA expression of gluconeogenic genes, and increased phosphorylation of AKT. Moreover, a single injection of IL-6 improved glucose tolerance, decreased hepatic gluconeogenic gene expression, and increased hepatic phosphorylation of AKT in lean and obese mice [80].

IL-6 AS A REGULATOR OF METABOLISM THROUGH AMPK

Knowledge of the role of IL-6 signalling in metabolic regulation is lacking and there are still many unknown interesting aspects. AMP-activated protein kinase (AMPK) appears to play a key role in the effects of IL-6 on metabolism. This protein has the function of acting as a sensor of the energy state in cells, stimulating pathways involved in energy production and turning off those where it is consumed. AMPK is a heterotrimeric complex with a catalytic subunit (α) and two regulators (β and γ), which controls the ATP/AMP ratio in the cell, with AMP being an allosteric activator of AMPK. Phosphorylation at threonine residue 172 of the α subunit by kinases, such as LKB1 when AMP concentration rises or CaMKKβ in the presence of Ca^{+2}, also activates AMPK, which can phosphorylate various proteins and regulate transcription of genes that participate in the regulation of metabolism, by activating catabolic pathways and turning off anabolic pathways [81].
L6 myotubes treated with IL-6 and 5-aminoimidazole-4-carboxamide riboside (AICAR), one of the main AMPK agonists, have both been shown to increase palmitate oxidation compared to control group. Therefore, increased fatty acid oxidation has a positive effect on energy production induced by IL-6 and AMPK [67].

TREATMENT WITH IL-6 AS AN ANTI-INFLAMMATORY AGENT

Treatments for different pathologies with chronic inflammation, such as rheumatoid arthritis, juvenile idiopathic arthritis, and Crohn's disease, have focused on drugs that interfere with IL-6 and IL-6R function [82,83]. Recently, tocilizumab, a monoclonal anti-IL-6 receptor antibody, was used to treat COVID, resulting in an improvement in the hyperinflammatory state associated with severe COVID [84]. It is interesting to note that some new studies are focussing on the anti-inflammatory action of IL-6-related treatments. A recent study at phase II clinical stage was established based on the hypothesis that soluble gp130 inhibits IL-6 *trans*-signalling without affecting canonical IL-6 signalling [85]. Indeed, it has been suggested that treatment with soluble gp130 is superior to that with drugs which target IL-6, because blocking IL-6 *trans*-signalling does not compromise canonical IL-6 signalling and therefore the body's defence against bacterial infections [85]. The action of soluble gp130 is important as it only inhibits the *trans*-signalling pathway, however, the canonical IL-6 pathway is believed to activate subsequent anti-inflammatory processes.

Additionally, inhibition of IL-6/sIL-6R *trans*-signalling has been proposed as a treatment for the COVID-19 cytokine storm. Although the effect of treatments that inhibit IL-6 may be unclear, pre-clinical models show that tocilizumab may reduce vascular dysfunction [86]. For other pathologies, such as cancer and coronary heart disease, the role of IL-6 is under investigation and new therapies may be proposed [87, 89]. In the case of coronary heart disease, in vascular endothelial cells, the pathways induced by IL-6 classic signalling and *trans*-signalling in these cells are distinct but overlap with different biological effects. *In vitro* and *in vivo* studies on the inhibition of IL-6 *trans*-signalling and activation of classic signalling demonstrate a cytoprotective effect [87]. Studies in transgenic mice expressing high levels of soluble gp130, inhibiting *trans*-signalling, have shown that gp130 plays an important role in the development of cancer, however, further studies are needed to determine exactly which mechanisms of the classic pathway are involved that could be targeted to treat this pathology [88]. In addition, it is important to mention that this type of therapy should also be investigated for metabolic diseases due to the significant role of IL-6 in the regulation of lipid and carbohydrate metabolism.

CONCLUSIONS

IL-6 is a cytokine that plays an important anti-inflammatory role in the body's response to endogenous and exogenous threats. The effect of IL-6 on metabolism of carbohydrates and lipids is an important factor in the different chronic inflammatory pathologies. Hence, continued study of this pleiotropic cytokine is important in order to understand its effect on signalling pathways and cellular function, as a potential target for the treatment of various metabolic disorders.

DISCLOSURE

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