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REVIEW

IL-6 signalling pathways and the development of type 2 diabetes

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Abstract
Interleukin 6 (IL-6), a multifunctional cytokine, has been implicated in the pathophysiology of type 2 diabetes (T2D). The elevated circulating level of IL-6 is an independent predictor of T2D and is considered to be involved in the development of inflammation, insulin resistance and β-cell dysfunction. On the other hand, an increasing number of evidence suggests that IL-6 has an anti-inflammatory role and improves glucose metabolism. The complex signal transduction mechanism of IL-6 may help explain the pleiotropic nature of the cytokine. IL-6 acts via two distinct signalling pathways called classic signalling and trans-signalling. While both signalling modes lead to activation of the same receptor subunit, their final biological effects are completely different. The aim of this review is to summarize our current knowledge about the role of IL-6 in the development of T2D. We will also discuss the importance of specific blockade of IL-6 trans-signalling rather than inhibiting both signalling pathways as a therapeutic strategy for the treatment of T2D and its associated macrovascular complications.

Keywords Type 2 diabetes · IL-6 · Classic signalling · Trans-signalling

Introduction

Interleukin 6 (IL-6) is a cytokine which was originally identified as a B cell differentiation factor (Hirano et al. 1985). Numerous cell types including immune cells, endothelial cells, skeletal and smooth muscle cells, thyroid cells, fibroblasts, mesangial cells, keratinocytes, microglial cells, astrocytes, certain tumor cells and islet β-cells have been reported to produce IL-6 (Kamimura et al. 2003). In general, IL-6 is involved in inflammatory and immunological processes, hematopoiesis, liver and neuronal regeneration (Rothaug et al. 2016; Scheller et al. 2006). IL-6 synthesis and secretion are induced during inflammatory conditions such as upon stimulation of Toll-like receptor (TLR) by lipopolysaccharide or upon stimulation of cells by interleukin 1 (IL-1) or tumor necrosis factor (TNF). IL-6 influences various cell types and has both pro- and anti-inflammatory characteristics (Hunter and Jones 2015). Dysregulation of IL-6 signalling has been implicated in the pathogenesis of several autoimmune and inflammatory diseases including type 2 diabetes (T2D) (Kamimura et al. 2003). It has been suggested that IL-6 promotes insulin resistance and contributes to the development of T2D. However, due to its different actions in distinct tissues, the role of IL-6 in the development of insulin resistance has been a subject of debate (Pedersen and Febbraio 2007). Here, we provide an overview of IL-6 signalling mechanisms, its controversial role in the pathogenesis of T2D and the rationale for the use of specific inhibitors of IL-6 trans-signalling in treatment of T2D.

IL-6 signalling

On target cells, IL-6 first binds to IL-6 receptor subunit α (IL-6R). The IL-6/IL-6R complex then associates with transmembrane signal transducing IL-6 receptor subunit β (gp130), which in turn induces gp130 dimerization and initiation of IL-6 intracellular signalling. IL-6 signal transduction through gp130 leads to the activation of Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK) and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathways inside cells (Fig. 1) (Hunter and Jones 2015; Schaper and Rose-John 2015).

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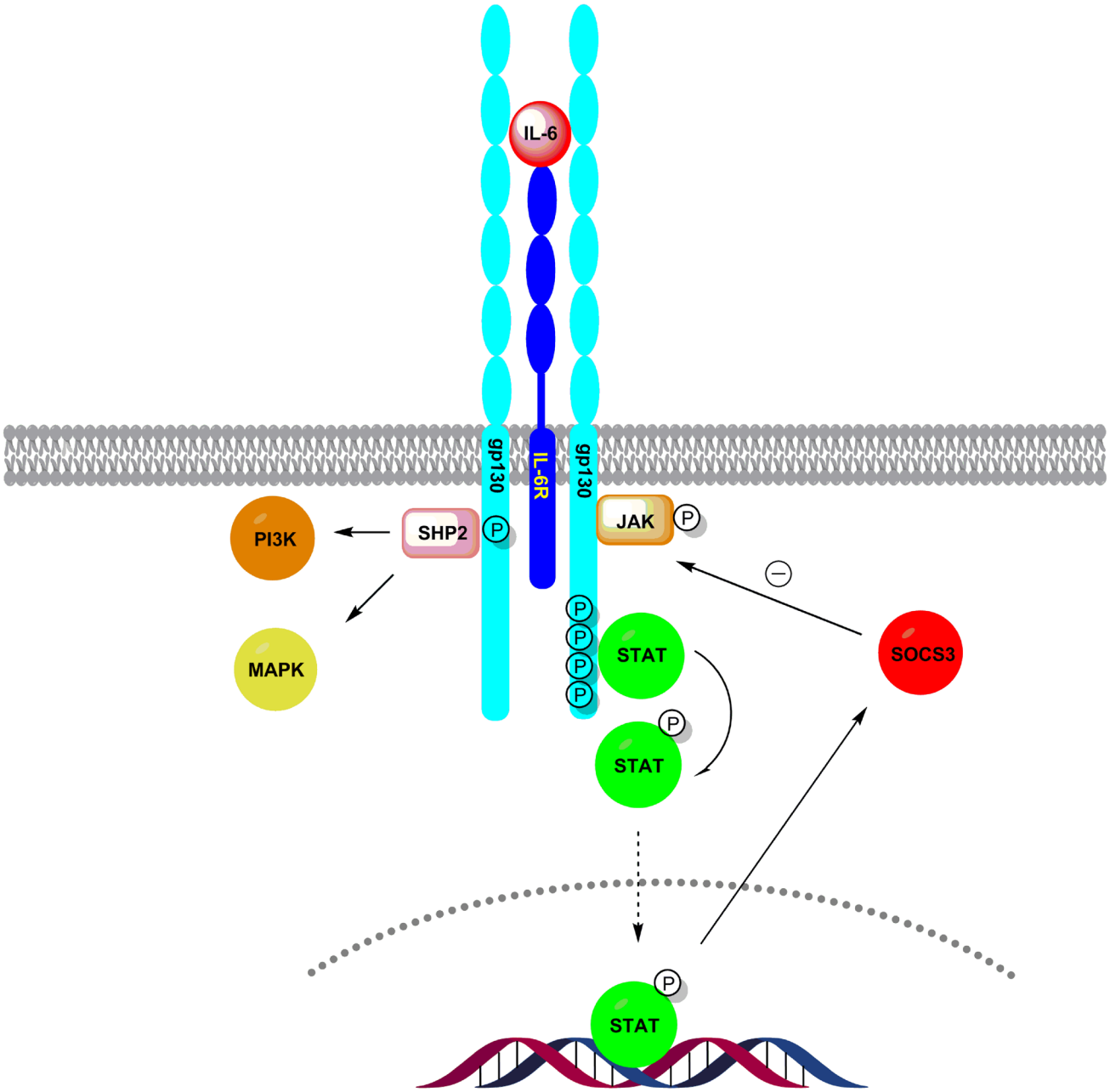

Fig. 1 IL-6 signalling A fully competent IL-6 receptor complex consists of IL-6, IL-6R and gp130. Formation of the IL-6/IL-6R/gp130 complex induces autophosphorylation and activation of the gp130-associated JAKs. These activated JAKs phosphorylate five tyrosine residues within the cytoplasmic portion of gp130. Phosphorylation of the membrane-proximal tyrosine residue, leads to the recruitment of SHP2, which then stimulates the activation of MAPK and PI3K pathways. Phosphorylation of the other tyrosine residues, in turn, leads to recruitment, phosphorylation, and translocation of STATs to the nucleus. In the nucleus, STATs bind to the DNA and induce the expression of various genes including acute phase proteins and the SOCS3 protein genes. SOCS3 inhibits JAKs, and therefore acts as a negative regulator of the gp130-associated signalling pathways

To mediate its biological effects, IL-6 utilizes two pathways termed classic and trans-signalling (Fig. 2). In classic signalling, IL-6 first binds to the membrane-bound non-signalling IL-6R (mbIL-6R). The IL-6/IL-6R complex associates with gp130 subunit and forms a signal transducing competent structure (Hunter and Jones 2015; Schaper and Rose-John 2015). While almost all cells in the body express gp130, mbIL-6R is only found on monocytes, macrophages, neutrophils, some types of T cells, hepatocytes, some epithelial cells, as well as, α- and β-cells of pancreatic islets (Ellingsgaard et al. 2008; Rose-John 2012; Schaper and Rose-John 2015). Since the receptor

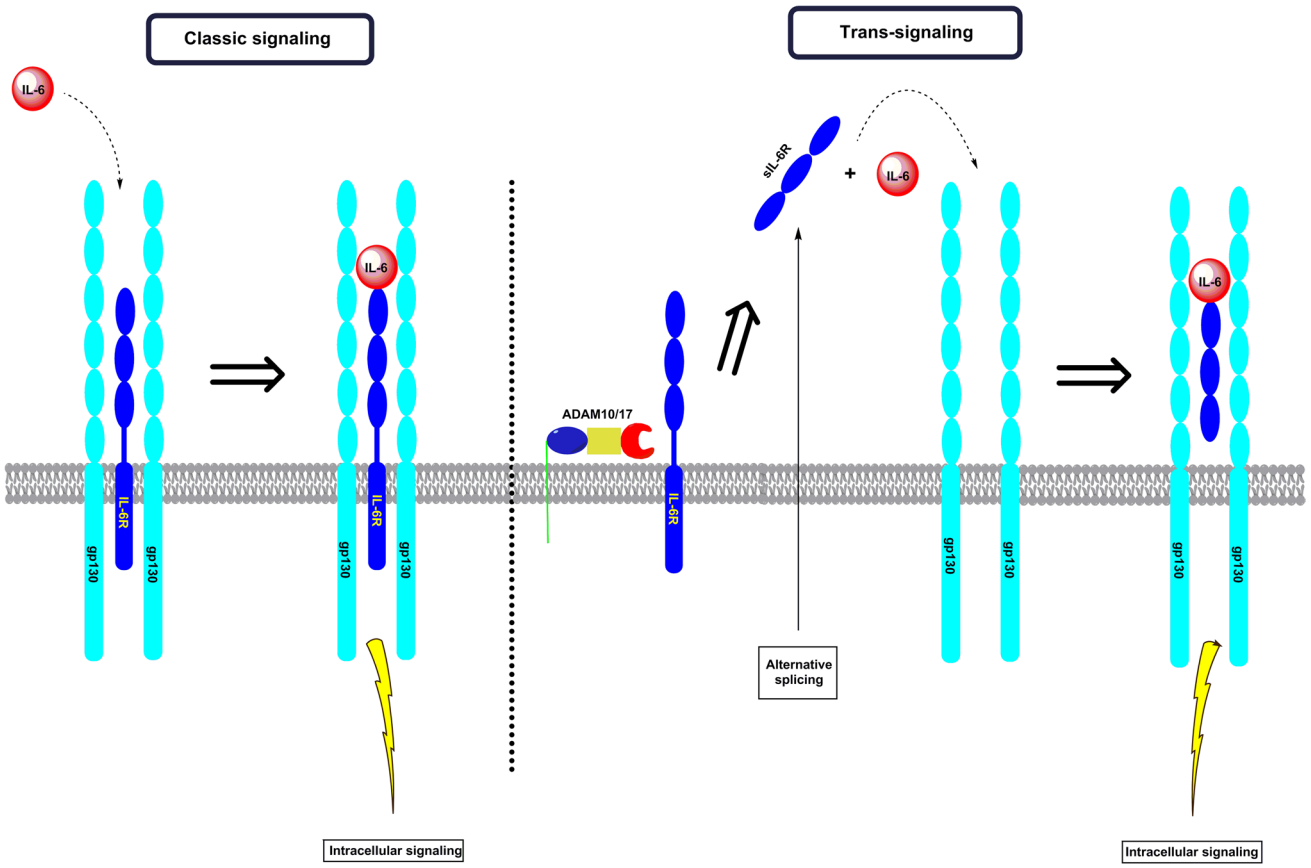

Fig. 2 Classic and trans-signalling of IL-6 In classic signalling, IL-6 binds to the membrane bound IL-6R. The IL-6/IL-6R complex associates with the signal transducing protein gp130, initiating intracellular signalling. In trans-signalling, a soluble form of IL-6R is proteolytically released by metalloprotease ADAM10/17 or by translation from an alternatively spliced *IL-6R* mRNA, and can bind IL-6 to form a complex that signals through gp130

subunit gp130 does not have any measurable affinity for IL-6 (Jostock et al. 2001), the majority of cells in the human body, which do not express IL-6R, are completely unresponsive to IL-6 (Fischer et al. 1997). Interestingly, IL-6R also exists in a soluble form (sIL-6R) comprising the extracellular portion of the receptor. In humans, sIL-6R is predominantly made by shedding of mbIL-6R, a process which is mediated by the metalloproteases ADAM10 and ADAM17 (Matthews et al. 2003). Furthermore, sIL-6R, to a lesser extent, can be generated by translation from an alternatively spliced IL-6R mRNA (Lust et al. 1992). SIL-6R can bind to IL-6, with an approximately similar affinity as mbIL-6R, to form an agonistic complex that signals through gp130 (Rose-John and Heinrich 1994). Even in the absence of mbIL-6R, the complex of IL-6 and sIL-6R can stimulate gp130 expressing cells and initiate the subsequent signalling (Taga et al. 1989). This process is called trans-signalling and due to the widespread expression of gp130 on almost every cell type, dramatically expands the spectrum of IL-6 target cells. While it is generally believed that IL-6 classic signalling is involved in the anti-inflammatory and regenerative activities of IL-6, IL-6 trans-signalling is considered to be responsible for the pro-inflammatory responses caused by this cytokine (Rose-John 2012; Schaper and Rose-John 2015).

Several soluble forms of gp130 (sgp130) are also present in the circulation. These soluble forms of gp130 are generated by translation from an alternatively spliced *IL6ST* mRNA. Sgp130 functions as a natural negative regulator of IL-6 trans-signalling (Narazaki et al. 1993). While sgp130 does not bind IL-6 or IL-6R alone, it interacts with the IL-6/sIL-6R complex and specifically blocks IL-6 trans-signalling, without affecting classical IL-6 signalling. High circulating levels of sgp130 in complex with IL-6 and sIL-6R are found in the serum of healthy individuals. It appears that sIL-6R and sgp130 constitute a physiological buffer for circulating IL-6, in order to prevent a systemic response to IL-6 trans-signalling. Once IL-6 is released into the circulation, it binds to sIL-6R. The IL-6/sIL-6R complex then associates with sgp130, which results in inhibition of systemic IL-6 trans-signalling. During some inflammatory conditions, however, plasma IL-6 levels exceed the levels of sgp130,

thus IL-6 can act systemically via trans-signalling (Rose-John 2012).

IL-6 role in the pathogenesis of T2D

T2D is a metabolic disorder characterized by relative insulin deficiency, hyperglycemia, increased demand for insulin and β-cell dysfunction resulting in insufficient production of insulin (Stumvoll et al. 2005). Obesity, in particular excess visceral adiposity, could lead to the development of chronic low-grade inflammation (Van Greevenbroek et al. 2013). Increasing evidence indicates that a chronic low-grade inflammatory state is associated with the pathogenesis of T2D. This low-grade inflammation represents itself, among other things, by elevated circulating levels of inflammatory cytokines such as IL-6 (Van Greevenbroek et al. 2013). Systemic levels of IL-6 are elevated in T2D patients (Kado et al. 1999) and high concentrations of circulating IL-6 is considered to be an independent predictor of T2D (Spranger et al. 2003). There is also evidence indicating that certain polymorphisms in *IL-6* gene have a significant association with the incidence of T2D (Illig et al. 2004). The role of IL-6 in the development of insulin resistance and T2D is not yet clear. Some studies point to the deteriorating effect of IL-6 on insulin action (Klover et al. 2003; Lagathu et al. 2003), while others suggest that IL-6 is probably required to maintain glucose homeostasis (Matthews et al. 2010; Wallenius et al. 2002).

Insulin sensitive tissues and pancreatic islets

Given its well-known pro-inflammatory properties and following the observation that its systemic concentration is elevated in T2D patients, IL-6 was soon implicated in the development of T2D. In the past few years, several studies have provided clear evidence that IL-6, via its effect on insulin sensitive tissues and pancreatic islets, plays a significant role in the regulation of glucose metabolism. However, due to their controversial results, these studies failed to elucidate the exact role of IL-6 in the pathogenesis of T2D.

Adipose tissue

Insulin resistance in adipose tissue is an early and pivotal phenomenon in the development of T2D. Adipocytes and adipose tissue macrophages are the major sources of circulating IL-6 in T2D (Makki et al. 2013). It is of note that T2D patients have more visceral adipose tissue (VAT) than non-diabetics (Gallagher et al. 2009). VAT is characterized by high secretion of inflammatory cytokines such as IL-6 (Van Greevenbroek et al. 2013). These inflammatory cytokines may cause insulin resistance in adipose tissue and may be transported through the circulation, affecting more distant sites including the vessel walls, skeletal and cardiac muscle, kidneys and circulating leukocytes (Donath and Shoelson 2011). Research shows that short- and long-term treatment of adipocytes with IL-6 has different effects on insulin signalling (Table 1). Short-term treatment with IL-6 does not impair the effect of insulin in the adipose tissue of rats

Table 1 Effects of IL-6 on insulin signalling and glucose and lipid metabolism in adipocytes

Species	Setting	IL-6 concentration	Duration	Results	References
Mouse	In vitro	5000–25,000 U mL^{-1}	0–24 h	In 3T3-L1 adipocytes, glucose transport is enhanced after treatment with IL-6	Stouthard et al. (1996)
Mouse	In vitro	20 ng mL^{-1}	30 min to 24 h	In 3T3-L1 adipocytes, acute IL-6 treatment (30 min) has no inhibitory effect on insulin signalling but long-term treatment (24 h) decreases the expression of IRS-1 and GLUT4	Rotter et al. (2003)
Mouse	In vitro	100 and 200 ng mL^{-1}	0–8 days	Treatment of 3T3-L1 and 3T3-F442A cells with IL-6 for 8 days decreases IR-β and IRS-1 expression, inhibits insulin-induced activation of IR-β, PKB, and ERK1/2; suppresses insulin-induced lipogenesis and glucose transport, and induces the overexpression of SOCS3	Lagathu et al. (2003)
Mouse	In vitro	30 ng mL^{-1}	16 h	Treatment with IL-6 inhibits expression and secretion of insulin-sensitizing adiponectin in 3T3-L1 cells	Fasshauer et al. (2003)
Rat	In vivo	0.85 nmol L^{-1} (total plasma level)	120 min	In adipose tissue IL-6 infusion for 120 min during euglycemic–hyperinsulinemic conditions, does not change the effect of insulin on glucose homeostasis	Rotter Sopasakis et al. (2004)
Human	In vitro	10 or 100 ng mL^{-1}	2 days	Treatment with IL-6 increases lipolysis in both subcutaneous and omental adipose tissues	Trujillo et al. (2004)

IRS insulin receptor substrate, *GLUT* glucose transporter, *IR-β* insulin receptor β, *PKB* protein kinase B, *ERK* extracellular-signal-regulated kinase, *SOCS* suppressor of cytokine signalling

(Rotter Sopasakis et al. 2004) and enhances glucose uptake in 3T3-L1 adipocytes (Stouthard et al. 1996). In contrast, chronic treatment with IL-6 induces insulin resistance, suppresses glucose transport and reduces insulin-induced lipogenesis in 3T3-L1 adipocytes (Lagathu et al. 2003; Rotter et al. 2003). Additionally, IL-6 has been shown to interfere with insulin signalling (Rotter et al. 2003) and increase lipolysis (Trujillo et al. 2004) in adipocytes. Several mechanisms have been suggested to be involved in IL-6-induced disruption of insulin signalling in adipocytes. Notably, chronically elevated IL-6 can increase the expression of suppressor of cytokine signalling 3 (SOCS3) (Lagathu et al. 2003). In adipocytes, SOCS3 overexpression is thought to inhibit insulin signalling by reducing the insulin-stimulated phosphorylation of insulin receptor β (IR-β), insulin receptor substrate 1 (IRS-1), protein kinase B (PKB/Akt), extracellular-signal-regulated kinase 1 (ERK1) and extracellular-signal-regulated kinase 2 (ERK2) (Fig. 3) (Lagathu et al. 2003). Moreover, negative effect on the expression of adiponectin, GLUT4, IRS-1, peroxisome proliferator-activated receptor gamma (PPAR-γ) and IR-β are among other potential mechanisms linked with IL-6-induced impairment of insulin actions in fat cells (Fasshauer et al. 2003; Lagathu et al. 2003; Rotter et al. 2003). Furthermore, exposure to TNF-α enhances the transcription of *IL-6* gene and thus contributes to the development of insulin resistance in adipocytes (Lagathu et al. 2003). In addition, IL-6 is responsible for macrophage recruitment to adipose tissue in obesity, which subsequently leads to the development of inflammation, insulin resistance and T2D (Fig. 3) (Kraakman et al. 2015).

Liver

In hepatocytes, the ability of IL-6 to modulate insulin signalling has been investigated by a number of independent studies (Table 2). In vitro studies demonstrated that acute treatment of human hepatocarcinoma cells and mouse hepatocytes with IL-6 inhibits insulin-stimulated tyrosine phosphorylation of IRS-1 and thus leads to the impairment of insulin signalling (Senn et al. 2002). These findings were further supported by in vivo experiments in which both acute and chronic exposure to IL-6 caused insulin resistance in mouse hepatocytes by reducing tyrosine phosphorylation of IRS-1 and IRS-2 (Kim et al. 2004; Klover et al. 2003). In line with these studies, Cai et al. found that injection of IL-6-neutralizing antibodies improves hepatic insulin sensitivity in mice (Cai et al. 2005). It has been suggested that mammalian target of rapamycin (mTOR), via regulation of

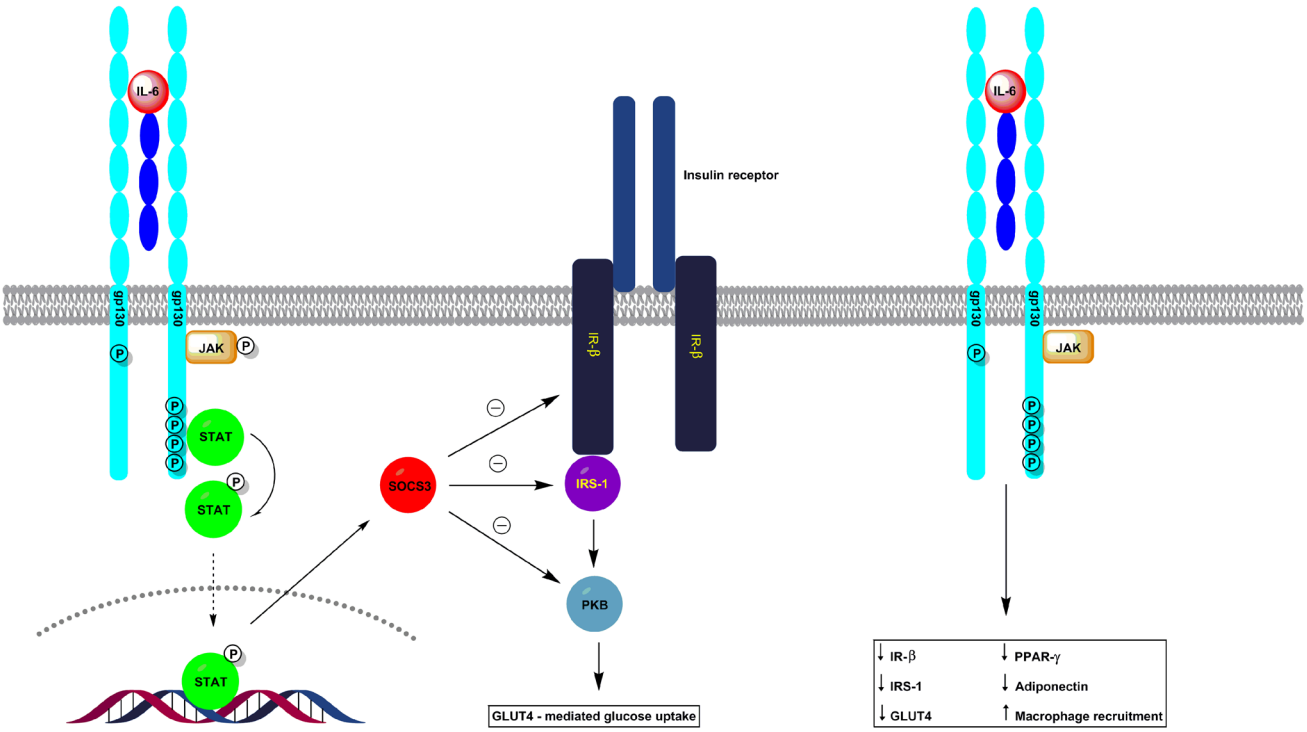

Fig. 3 Role of IL-6 in regulation of insulin signalling in adipocytes In adipocytes, elevated levels of IL-6 increase SOCS3 expression. SOCS3 negatively regulates insulin signalling by reducing the insulin-stimulated phosphorylation of IR-β, IRS-1, and PKB. Moreover, IL-6 impairs insulin action in adipocytes by decreasing the expression of insulin signalling components (IR-β, IRS-1, and GLUT4) and insulin-sensitizing factors (PPAR-γ and adiponectin). IL-6 can also induce macrophage recruitment to adipose tissue, which leads to the development of inflammation and subsequent disruption of insulin signalling

Table 2 Effects of IL-6 on insulin signalling and glucose metabolism in hepatocytes

Species	Setting	IL-6 concentration	Duration	Results	References
Human/mouse	In vitro	20 ng mL^{-1}	0–8 h	Exposure to IL-6 inhibits insulin receptor signal transduction and insulin action in human hepatocarcinoma HepG2 cells by decreasing tyrosine phosphorylation of IRS-1. The inhibitory effect is maximum after 1 h	Senn et al. (2002)
Mouse	In vivo	≈ 130 pg mL^{-1} (total plasma level)	5–7 days	Continuous infusion of IL-6 causes hepatic insulin resistance by reducing insulin receptor auto-phosphorylation and tyrosine phosphorylation of IRS-1 and IRS-2	Klover et al. (2003)
Mouse	In vivo	N/A	120 min	Infusion of 0.5 μg h^{-1} IL-6 reduces insulin-stimulated IRS-2-associated PI3K activity and causes insulin resistance in mouse hepatocytes	Kim et al. (2004)
Human	In vitro	20 ng mL^{-1}	2.5 h	Treatment of HepG2 cells with IL-6 induces hepatic insulin resistance. mToR plays a key role in this process	Kim et al. (2008)

IRS insulin receptor substrate, *STAT* signal transducer and activator of transcription, *SOCS* suppressor of cytokine signalling, *mTOR* mammalian target of rapamycin

STAT3 activation, could play a key role in IL-6-induced hepatic insulin resistance. Upon stimulation with IL-6, mTOR enhances STAT3 activation, which results in SOCS3 overexpression and subsequent inhibition of insulin signalling in liver cells (Fig. 4) (Kim et al. 2008). In contrast to the aforementioned data which point to IL-6 as a negative regulator of insulin action in the liver, results from several studies using transgenic strategies suggest a beneficial role of IL-6 in hepatic insulin action. For example, studies of IL-6-deficient mice (*IL-6*$^{-/-}$) showed that the absence of IL-6 leads to the development of inflammation and insulin resistance in the liver (Matthews et al. 2010). In addition,

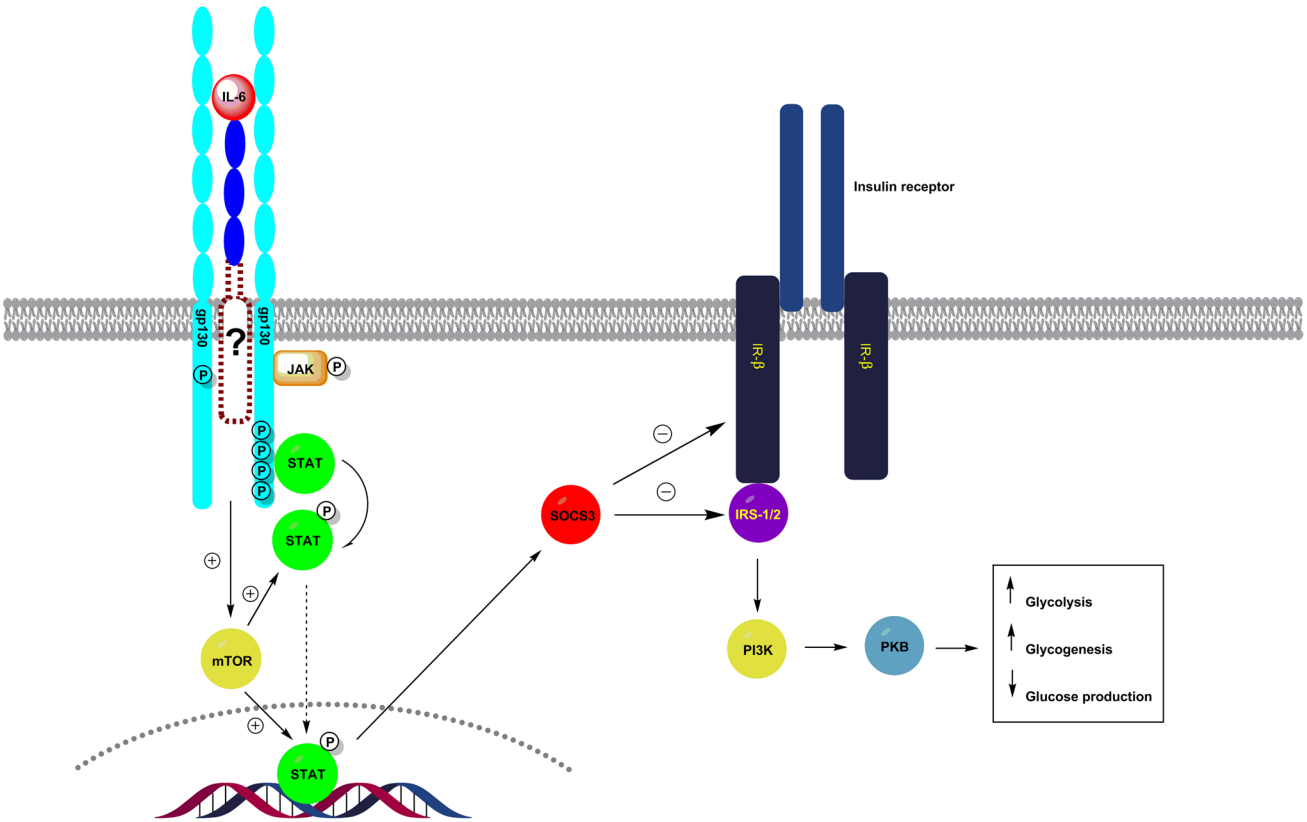

Fig. 4 Role of IL-6 in regulation of hepatic insulin signalling In hepatocytes, mTOR upon IL-6 stimulation, enhances the activity of STAT and increases SOCS3 expression. SOCS3 negatively regulates insulin signalling which leads to the development of insulin resistance in the liver. Note that in cells such as hepatocytes, which express IL-6R, IL-6 could act via both classic and trans-signalling

mice with hepatocyte-specific IL-6R deficiency displayed enhanced secretion of inflammatory cytokines by Kupffer cells, which led to the development of systemic inflammation and insulin resistance in the liver, skeletal muscle and white adipose tissue, suggesting that hepatic IL-6 signalling limits the expression of inflammatory cytokines in the liver and contributes to the improvement of both local and systemic insulin sensitivity (Wunderlich et al. 2010).

Skeletal muscle

It is now well-known that exercise can significantly induce the production and release of IL-6 into the circulation by skeletal muscles (Steensberg et al. 2000). The acute elevation of plasma IL-6 is followed by increased plasma levels of anti-inflammatory interleukin 10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra). IL-10 and IL-1ra are known to have inhibitory effects on the production of pro-inflammatory cytokines TNF-α and IL-1, respectively (Pedersen and Febbraio 2008). Therefore, it appears that exercise-induced release of IL-6 into the circulation, through promoting an anti-inflammatory environment, plays a protective role against systemic inflammation and leads to the improvement of global insulin sensitivity. Regarding the effects of IL-6 on skeletal muscles, IL-6 treatment has been shown to increase the translocation of GLUT4 to plasma membrane and promote insulin-stimulated glucose uptake in rat myotubes (Carey et al. 2006). As this effect of IL-6 was abolished in AMP-activated protein kinase (AMPK) dominant-negative-infected cells, IL-6 action on glucose metabolism of skeletal muscles was suggested to be mediated by AMPK (Carey et al. 2006). Moreover, both acute and chronic exposure to IL-6 resulted in increased glucose uptake in human skeletal muscle cells (Al-Khalili et al. 2006; Glund et al. 2007). Another study conducted by Weigert et al. showed that short-term exposure to IL-6, by inducing a rapid recruitment of IRS-1 to the IL-6 receptor complex and activation of IRS-1/Akt signalling, results in the improvement of insulin action in mouse skeletal muscle (Weigert et al. 2006). The same study reported that induction of SOCS3 expression by IL-6, which is thought to be an important mechanism for IL-6-mediated reduction of insulin action in both adipocytes and hepatocytes, does not occur in skeletal muscle cells (Weigert et al. 2006). In contrast to these findings, Kim et al. demonstrated that IL-6 infusion in mice inhibits insulin-stimulated IRS-1-associated PI3K activity, and therefore reduces insulin-stimulated glucose uptake in skeletal muscle (Kim et al. 2004). Moreover, chronically elevated levels of IL-6, by activation of c-Jun N-terminal kinase (JNK), accumulation of SOCS3 and protein tyrosine phosphatase1B (PTP1B) activity increase results in decreased insulin-stimulated glucose uptake in murine skeletal muscle cells (Table 3) (Fig. 5) (Nieto-Vazquez et al. 2008).

Pancreatic islets

The progression from insulin resistance to T2D implicates a failure of pancreatic β-cells to compensate for the increased insulin demand. Under conditions of metabolic stress (elevated glucose and/or palmitate) and T2D, IL-6 levels are increased in human and mouse islets (Böni-Schnetzler et al. 2009; Ehses et al. 2007). This indicates that in addition to systemic increase of IL-6, local islet IL-6 levels are also elevated in T2D, suggesting a potential role of IL-6 in pancreatic islets under this condition. Long-term treatment of rodent islets with IL-6 impairs glucose-stimulated insulin secretion (Ellingsgaard et al. 2008). Moreover, IL-6 regulates the proliferation and apoptosis of pancreatic α- and β-cells. IL-6 induces the proliferation of both α- and β-cells. However, this cytokine exerts distinct effects on α- and β-cell apoptosis. In islet cells treated with high levels of glucose and palmitate, the presence of IL-6 protects α-cells from apoptosis, whereas β-cell apoptosis is exaggerated in the presence of IL-6 (Ellingsgaard et al. 2008). Furthermore, elevation of plasma IL-6 was recently found to stimulate pancreatic α-cells to secrete glucagon-like peptide-1 (GLP-1). GLP-1 is a hormone which induces insulin secretion by β-cells and thus results in improved glycemic parameters (Table 4) (Ellingsgaard et al. 2011). Interestingly, following high fat diet (HFD) feeding, IL-6 knockout mice are unable to expand their α-cell mass and show increased glycemia caused by impaired insulin secretion. These results suggest that systemically elevated levels of IL-6 in response to HFD, which leads to an α-cell expansion and subsequent increase in GLP-1 production, may be an adaptive response to maintain proper insulin secretion by β-cells (Fig. 6a) (Ellingsgaard et al. 2008, 2011). Overall, although the deleterious effect of elevated IL-6 on glucose homeostasis in pancreatic islets cannot be ignored, it appears that the role of IL-6 in the regulation of α-cells may compensate for the impaired β-cells function in T2D and contributes to limit hyperglycemia.

In summary, the above-mentioned data are suggestive of a tissue-specific and context-dependent effect of IL-6 on the regulation of glucose homeostasis. The final effect of IL-6 on insulin sensitive tissues seems to be dependent on several factors such as its concentration (high or low), kinetics (acute or chronic) and source. In addition, certain metabolic stressors (e.g. glucose and free fatty acids) and inflammatory mediators (e.g. cytokines and chemokines) can regulate IL-6 signalling and thus affect how IL-6 acts in different conditions. Furthermore, given the anti-inflammatory and insulin-sensitizing effects of IL-6, it is possible that elevated levels of IL-6 in T2D patients represent a compensatory mechanism in order to reduce inflammation and maintain proper glucose homeostasis. The latter view is further supported by studies using transgenic mice, which suggest that IL-6

Table 3 Effects of IL-6 on insulin signalling and glucose metabolism in skeletal muscle

Species	Setting	IL-6 concentration	Duration	Results	References
Mouse	In vivo	N/A	120 min	Infusion of 0.5 μg h^{-1} IL-6 reduces insulin-stimulated IRS-1-associated PI3K activity, and reduces insulin-stimulated glucose uptake in skeletal muscle	Kim et al. (2004)
Rat	In vitro	100 ng mL^{-1}	120 min	IL-6 treatment results in increased translocation of GLUT4 to plasma membrane and promotes insulin-stimulated glucose uptake in L6 myotubes	Carey et al. (2006)
Human	In vitro	25 ng mL^{-1}	20 min, 3 h, and 8 days	IL-6 treatment for 3 h and 8 days increases glucose uptake	Al-Khalili et al. (2006)
Human/rat/mouse	In vitro	20 ng mL^{-1}	5–120 min	Treatment with IL-6 improves insulin action in human skeletal muscle cells, rat L6 myotubes, and murine C2C12 myoblasts	Weigert et al. (2006)
Mouse	In vivo	≈ 60 pg mL^{-1} (total plasma level)	30 and 60 min	Muscle and liver cells express SOCS-3 differently in response to IL-6	Weigert et al. (2006)
Human	In vitro	120 ng mL^{-1}	80 min	Treatment with IL-6 increases glucose uptake, glycogenesis, and glucose oxidation in skeletal muscle cells	Glund et al. (2007)
Mouse/rat	In vitro	20 ng mL^{-1}	3 and 24 h	IL-6 treatment for 3 h, increases glucose uptake in C2C12 myotubes, while IL-6 treatment for 24 h impairs insulin-stimulated glucose uptake	Nieto-Vazquez et al. (2008)

IRS insulin receptor substrate, *GLUT* glucose transporter

is needed to counteract the increased inflammation and the absence of IL-6 could impair insulin signalling. Finally, as mentioned previously, the physiological responses to classic and trans-signalling of IL-6 are completely different from each other. Therefore, presence or lack of mbIL-6R on target cells, as well as, relative levels of sIL-6R and sgp130 could also influence the biological outcomes of exposure to IL-6.

Immune cells

Immune cells are considered as both sources and targets of IL-6 (Table 5). Studies have shown that interactions between IL-6 and the components of innate and adaptive immune systems play a major role in the development of low-grade chronic inflammation in T2D.

Innate immune cells

Macrophages are central mediators of inflammation in T2D. These cells are generally classified into two distinct subtypes: the classically activated macrophages termed M1, which mainly secrete pro-inflammatory cytokines including IL-6 and the alternatively activated macrophages termed M2, which produce anti-inflammatory cytokines (Chawla et al. 2011). In T2D, macrophage infiltration into insulin sensitive tissues and pancreatic islets, as well as, macrophage polarization toward the M1 phenotype in these tissues increase and contribute to the development of an inflammatory state (Esser et al. 2014). In addition to macrophages, the number of mast cells also increases in adipose tissue of obese humans and mice. These cells exacerbate insulin resistance and promote glucose intolerance by producing IL-6 and interferon-γ (Liu et al. 2009). Furthermore, neutrophils play an important part in the regulation of IL-6 signalling during inflammatory states. Neutrophils are among the first cells to accumulate at the sites of inflammation. These cells have a short life-span and die rapidly via apoptosis. In inflammatory conditions, apoptosis induces shedding of IL-6R from neutrophils. This process facilitates the formation of IL-6/sIL-6R complex and promotes IL-6 trans-signalling in smooth muscle cells, endothelial cells, mesothelial cells, epithelial cells and fibroblasts (Hunter and Jones 2015; Rose-John et al. 2017).

Adaptive immune cells

Cells of the adaptive immune system are also involved in adipose tissue inflammation and insulin resistance. Several studies have demonstrated a role for T cell subset imbalance in tissue inflammation. In general, it appears that the number of $CD8^+$ T cells and $CD4^+$ T helper 1 (T_H1) cells increase in obese adipose tissue. The expansion of $CD8^+$ T

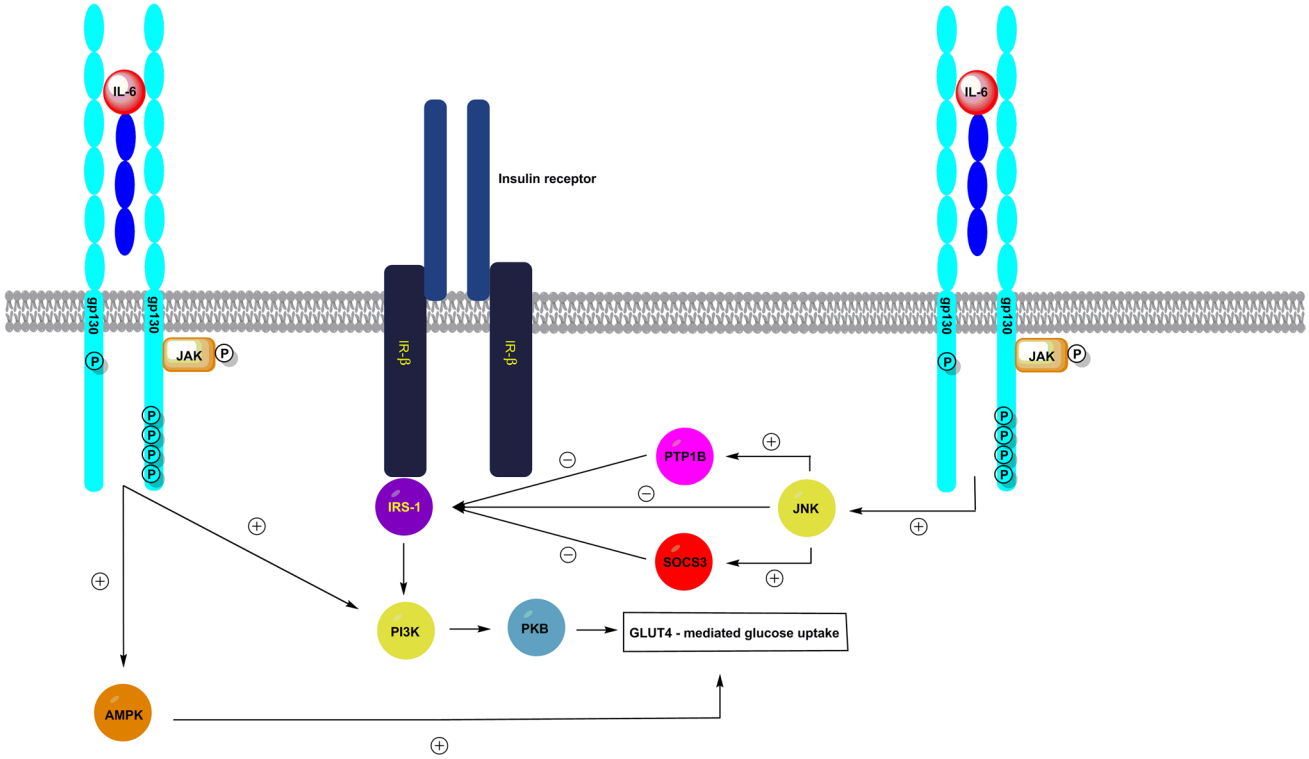

Fig. 5 Dual role of IL-6 in regulation of insulin signalling and glucose metabolism in skeletal muscle In skeletal muscle, IL-6 enhances glucose uptake via stimulating the activity of AMPK and PI3K. IL-6 could also negatively affect insulin action in a JNK-dependent manner. Serine phosphorylation of IRS-1 by JNK impairs insulin signalling. Moreover, JNK increases PTP1B activity and SOCS3 expression. Tyrosine dephosphorylation of IRS-1 by PTP1B and impairment of tyrosine phosphorylation of IRS-1 by SOCS3 lead to decreased insulin-stimulated glucose uptake in skeletal muscle

cells and T_H1 cells stimulate the M1 polarization of macrophages. As discussed earlier, M1 macrophages secrete pro-inflammatory cytokines such as IL-6 and further contribute to the progression of inflammation and insulin resistance (Feuerer et al. 2009; Nishimura et al. 2009; Winer et al. 2009). In addition to pro-inflammatory T cells, the number of B cells also increases in visceral adipose tissue of obese mice (Winer et al. 2011). B cells from obese mice secrete high amounts of pro-inflammatory cytokines such as IL-6 (DeFuria et al. 2013). As a result, B cells enhance the activation and differentiation of adipose tissue pro-inflammatory T cells, which in turn leads to M1 macrophage polarization and insulin resistance. In addition, it is also possible that B cell-produced antibodies and cytokines directly affect insulin sensitivity in adipocytes (Winer et al. 2011).

Circulating leukocytes

While IL-6 mRNA expression is increased in peripheral blood mononuclear cells (PBMCs) of hypertensive T2D patients (Navarro-Gonzalez et al. 2010) and type 2 diabetic women (Tsiotra et al. 2008), induced hyperglycemia has been shown to decrease *IL-6* gene transcription (Spindler et al. 2016). Moreover, a study conducted by Pickup et al. demonstrates that, despite the elevated levels of plasma IL-6, the production of this cytokine by blood cells of T2D patients is lower than nondiabetics (Pickup et al. 2000).

IL-6 signalling as a therapeutic target for treatment of T2D

Data from several studies suggest that IL-6 contributes to the onset and progression of chronic inflammation and autoimmunity (Tanaka et al. 2014). The pathological role of IL-6 is further supported by experiments whereby IL-6 blockade (using anti-IL-6 or anti-IL-6R antibodies, or IL-$6^{-/-}$ mice) demonstrated preventive and suppressive effects on the development of various immune-related disorders. Notably, the humanized anti-IL-6R antibody tocilizumab has been approved for the treatment of Rheumatoid Arthritis (RA) in more than 100 countries. Tocilizumab inhibits the binding of IL-6 to both mbIL-6R and sIL-6R and thereby results in complete blockade of IL-6 signalling (Tanaka et al. 2012, 2014). In addition to RA, tocilizumab and other anti-IL-6R antibodies have shown promising results in the treatment

Table 4 Effects of IL-6 on pancreatic islets insulin production

Species	Setting	IL-6 concentration	Duration	Results	References
Human/mouse	In vitro	1, 10, 100 ng mL^{-1}	1 h	Treatment of human and mouse islets with IL-6 does not affect insulin secretion	Ellingsgaard et al. (2008)
Human	In vitro	200 ng mL^{-1}	2–96 h	Treatment of human islets with IL-6 does not affect insulin secretion	Ellingsgaard et al. (2008)
Mouse	In vitro	100 ng mL^{-1}	12 h	Treatment of α- and β-cells with elevated levels of glucose and palmitate, in the presence of IL-6, significantly decreases α-cell apoptosis, whereas exaggerates β-cell apoptosis	Ellingsgaard et al. (2008)
Mouse	In vitro	100 ng mL^{-1}	2, 3, and 4 days	4-day treatment of mouse islets with IL-6 reduces glucose-stimulated insulin secretion	Ellingsgaard et al. (2008)
Rat	In vitro	100 ng mL^{-1}	48 h	Treatment with IL-6 induces the proliferation of both α- and β-cells after 48 h	Ellingsgaard et al. (2008)
Mouse	In vitro	100 ng mL^{-1}	24 and 96 h	Treatment with IL-6 induces the proliferation of α- and β-cells after 24 and 96 h, respectively	Ellingsgaard et al. (2008)
Mouse	In vivo	100 ± 20 pg mL^{-1} (total plasma level)	90 min	Systemically elevated IL-6 concentration in response to 90 min of exercise increases GLP-1 secretion from α-cells	Ellingsgaard et al. (2011)
Mouse	In vivo	10–550 pg mL^{-1} (total plasma level)	15 min	Injection of 40 and 400 ng of IL-6 increases insulin secretion along with plasma concentrations of GLP-1	Ellingsgaard et al. (2011)
Mouse	In vivo	≈ 10–550 pg mL^{-1} (total plasma level)	7 days	Twice daily injections of 400 ng of IL-6 decrease both fasting and fed plasma glucose and increase fasting plasma concentrations of GLP-1	Ellingsgaard et al. (2011)
Human	In vitro	200 ng mL^{-1}	4 days	Treatment of human islets with IL-6 increases GLP-1 secretion	Ellingsgaard et al. (2011)

GLP glucagon-like peptide

of several immune-related disorders (Tanaka et al. 2014; Waetzig and Rose-John 2012). For example, tocilizumab has been reported to improve insulin sensitivity and decrease glycated hemoglobin (HbA_1c) levels in humans (Ogata et al. 2010; Schultz et al. 2010). Taken together, these findings support the idea that IL-6 signalling is a potential therapeutic target for the treatment of inflammatory-associated disorders including T2D.

However, as mentioned earlier, IL-6 is a truly multifunctional cytokine. Despite its role in the development of inflammation and insulin resistance, IL-6 is also involved in the improvement of insulin sensitivity, insulin secretion, glucose homeostasis and suppression of inflammatory processes in obesity and/or T2D. This pleiotropic behavior is closely related to whether IL-6 acts via its classic or trans-signalling mechanism. The effect of IL-6 on pancreatic islets, which in turn leads to increased insulin secretion by β-cells and improvement in glycemia is mediated through classic signalling (Ellingsgaard et al. 2008, 2011). Moreover, given the presence of mbIL-6R in hepatocytes, the beneficial effect of IL-6 on insulin sensitivity, glucose tolerance and inflammatory processes in the liver is most likely mediated by classic rather than trans-signalling of IL-6. On the other hand, IL-6 trans-signalling is involved in the infiltration of macrophages into expanding adipose tissue, resulting in the establishment of a chronic inflammatory state and insulin resistance in obese individuals (Kraakman et al. 2015). In addition, the lack of mbIL-6R on endothelial cells and vascular smooth muscle cells points to trans-signalling as the main mechanism involved in the deleterious effect of IL-6 on vasculature, which in turn could lead to atherosclerosis and various macrovascular complications in diabetics. IL-6 impairs the vasodilator effects of insulin in endothelial cells (Andreozzi et al. 2007). Additionally, IL-6, via trans-signalling,

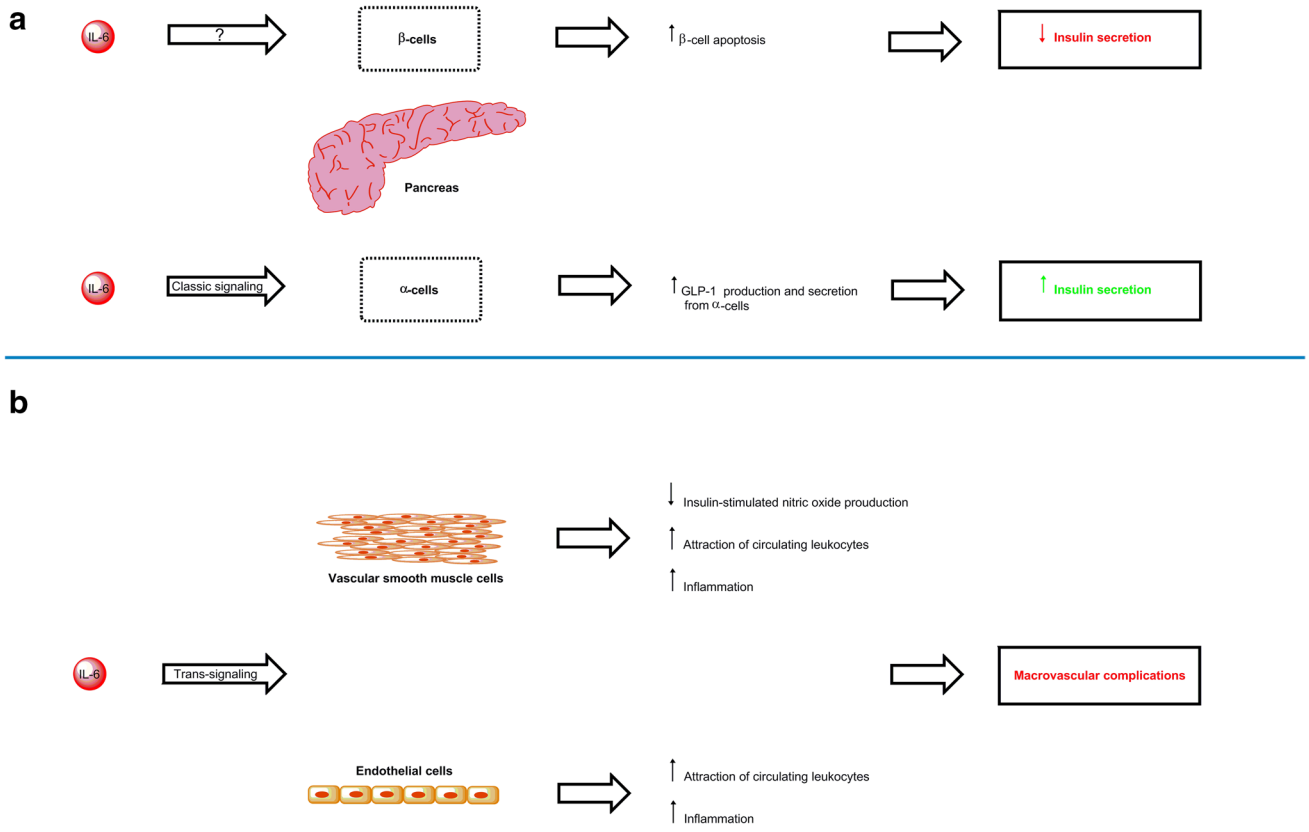

Fig. 6 Metabolic effect of IL-6 on pancreatic islets and its role in the development of macrovascular complications **a** Elevated IL-6 concentrations stimulate GLP-1 secretion from pancreatic α-cells, improving insulin secretion and glycemia; a mechanism which may be involved in β-cell compensation for insulin resistance in T2D patients. **b** The effect of IL-6 on vascular smooth muscle cells and endothelial cells via trans-signalling leads to atherosclerosis and various macrovascular complications in diabetic patients

Table 5 IL-6 effects on immune cells

Cell type	IL-6 production	Effects of IL-6 stimulation	Reference(s)
Neutrophils	Yes	Enhances chemotaxis in response to IL-8; conflicting reports on neutrophil apoptosis	Afford et al. (1992), Biffl et al. (1995), Wright et al. (2014)
Monocytes and macrophages	Yes	Promotes M2 polarization by inducing the expression of IL-4R; switches monocyte differentiation to macrophages rather than DCs	Chomarat et al. (2000), Mauer et al. (2014)
Dendritic cells	Yes	Inhibits activation of NF-κB and expression of CCR7	Hegde et al. (2004)
B cells	Yes	Induces the maturation of B cells into plasma cells	Hirano et al. (1985)
T cells	Yes	Controls the expansion of T_H1 cells, differentiation of T_H17 and cytotoxic T cells from naive T cells	Acosta-Rodriguez et al. (2007), Fielding et al. (2014), Takai et al. (1988)

IL-8 interleukin 8, *IL-4R* interleukin 4 receptor, *DC* dendritic cells, *NF-κB* nuclear factor-κB, *CCR7* C–C chemokine receptor type 7, *T_H1 cell* type 1 T helper cell, *T_H2 cell* type 2 T helper cell, *T_H17 cell* type 17 T helper cell, *Treg cell* regulatory T cell

promotes the secretion of various chemokines and adhesion molecules in both endothelial and vascular smooth muscle cells, leading to the attraction of circulating leukocytes and consequent resolution of inflammatory reactions (Fig. 6b) (Klouche et al. 1999; Romano et al. 1997).

From these data it can be concluded that IL-6 trans-signalling through sIL-6R is mainly associated with pro-inflammatory and harmful actions of the cytokine in the pathogenesis of T2D. Conversely, classic signalling via mbIL-6R is mostly linked with anti-inflammatory and regenerative activities of IL-6 and probably has a beneficial effect on glucose metabolism. Tocilizumab and many other IL-6R antibodies block both classic and trans-signalling of IL-6. This global inhibition of IL-6 signalling pathways, disrupts both

pro- and anti-inflammatory activities of the cytokine and may result in various physiological dysfunctions. Moreover, global IL-6 blockade has been associated with increased risk of bacterial infections, liver malfunction, elevation of cholesterol and weight gain (Tanaka et al. 2012; Waetzig and Rose-John 2012). These findings have led to the suggestion that specific inhibition of trans-signalling, as compared to the global inhibition of IL-6, may result in better therapeutic outcomes with fewer undesired side effects.

The sgp130Fc protein is a recombinant version of sgp130, which consists of the extracellular portion of gp130 fused to the Fc region of a human immunoglobulin G1 (IgG1) antibody. Sgp130Fc specifically blocks IL-6 trans-signalling, without affecting classical IL-6 signalling. Therefore, sgp130 inhibits the pro-inflammatory actions of IL-6, while leaving its anti-inflammatory and protective activities intact. Sgp130Fc has demonstrated robust efficacy in the treatment of many autoimmune and inflammatory diseases, with better side effect profile than global blockers of IL-6 signalling (Rose-John 2012; Waetzig and Rose-John 2012). Sgp130Fc selectively blocks the chemotactic signalling mediated by sIL-6R, therefore prevents HFD induced-macrophage infiltration into obese adipose tissue (Kraakman et al. 2015). In addition, treatment with sgp130Fc significantly reduces atherosclerosis, decreases expression of endothelial adhesion molecules and intimal smooth muscle cell infiltration, thus reduces monocyte recruitment and the subsequent progression of atherosclerotic plaques (Schuett et al. 2012). Moreover, none of the adverse effects of complete IL-6 blockade was demonstrated with sgp130Fc (Kraakman et al. 2015; Rose-John 2012; Schuett et al. 2012).

The above-mentioned data clearly highlight the therapeutic potential of selective inhibition of IL-6 trans-signalling for treatment of T2D and its vascular complications. Furthermore, given the specificity of sgp130Fc to inhibit trans-signalling, this protein can be used as a molecular tool to identify whether a certain effect of IL-6 (e.g. effect of IL-6 on glucose metabolism) is mediated via classic or trans-signalling (Rose-John 2012). This approach could be particularly useful to study the signalling pathways of IL-6 in mb-IL-6R expressing cells (e.g. hepatocytes and pancreatic islet cells), which can be stimulated by both the classic and trans-signalling pathways. Therefore, in addition to its therapeutic properties, the sgp130Fc protein allows us to discriminate between different IL-6 signalling pathways and thus advance our knowledge on the pathophysiological role of IL-6 signalling in the development of T2D.

Conclusion

Dysregulation of IL-6 production is associated with the pathogenesis of T2D. However, the effects of IL-6 on insulin sensitivity and glucose metabolism are markedly divergent in different tissues and contexts. This pleiotropic nature is at least in part dependent on the signalling pathway which is activated by IL-6. Increasing evidence from clinical and animal studies suggest that, in many inflammatory conditions, selective blockade of trans-signalling is therapeutically more effective and safer than global inhibition of IL-6, supporting the concept that pro-inflammatory and harmful activities of the cytokine are mainly mediated via trans-signalling. Of particular note, the sgp130Fc protein, which is a specific inhibitor of IL-6 trans-signalling, has been shown to completely prevent macrophage infiltration into obese adipose tissue and significantly reduce the extent of atherosclerosis. These results indicate that specific blockade of IL-6 trans-signalling with sgp130Fc could be considered as a potential therapeutic strategy for treatment of T2D and its macrovascular complications. In summary, although further investigations are needed to improve our knowledge about the complex molecular mechanisms of IL-6 signalling and its role in the development of T2D, inhibiting pro-inflammatory and deleterious effects of IL-6, without affecting its beneficial metabolic functions appears to be a tempting approach to deal with IL-6-associated disorders. Using sgp130Fc, which is the only available therapeutic agent for specific blockade of IL-6 trans-signalling, in combination with other anti-inflammatory treatments, such as anti-IL-1β agents, could lead to the development of more efficacious strategies for treatment of T2D.

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