Arch. Immunol. Ther. Exp. (2013) 61:119–125
DOI 10.1007/s00005-012-0210-1

REVIEW

Inflammation, Cytokines and Insulin Resistance: A Clinical Perspective

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Received: 17 May 2012 / Accepted: 20 December 2012 / Published online: 10 January 2013

Abstract Obesity and obesity-related disorders have dramatically increased globally in the last decades. These entities are commonly associated with a state of insulin resistance and the relationship between extensive lipid deposition and insulin resistance is widely accepted. The underlying mechanisms for insulin resistance, however, are still incompletely understood. Evidence from experimental research and human studies in the last years has suggested that innate immune pathways and inflammatory mechanisms also might play a role. Insulin resistance in case of obesity is commonly accompanied by low-grade systemic inflammation and adipose tissue inflammation. The expression of various pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 is increased in adipose tissue and its expression linked to systemic inflammation and accompanying insulin resistance. Weight loss reduces this enhanced cytokine expression in the adipose tissue and thereby improves systemic inflammation. Whereas there is also substantial evidence that pro-inflammatory cytokines, certain members of the inflammasome and various transcription factors such as nuclear factor-κB play a major role in animal models of insulin resistance and type 2 diabetes, human studies neutralizing certain pro-inflammatory cytokines suggest so far that not all pro-inflammatory cytokines are of equal clinical importance. First clinical studies favor an important role for IL-1 family members and probably IL-6 but not for TNF-α in insulin-resistant states. Although we still have missing links in the understanding of insulin resistance, certain inflammatory pathways have also evolved in humans as central players.

Keywords Innate immunity · Type 2 diabetes · Adipocytokines · Anti-cytokine therapies

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Introduction

Incidence of obesity and related disorders has risen dramatically over the last decades. Obesity is not only associated with the development of type 2 diabetes mellitus (T2D) and hypertension, but also impairs liver function leading to non-alcoholic fatty liver disease (NAFLD). Insulin resistance is the key primary defect underlying the development of T2D and is a central factor defining the metabolic syndrome, a disorder defined by obesity, hypertension, glucose intolerance, and dyslipidemia. The pathophysiology of insulin resistance is complex involving accumulation of various lipids in different locations, activation of the unfolded protein response/endoplasmic reticulum stress response and activation of various pathways of the innate immune response (Fu et al. 2012; Samuel and Shulman 2012). Insulin resistance has been identified in the last years as being frequently associated with a state of low-grade inflammation and therefore it is assumed that inflammation contributes in a substantial way to its development (Glass and Olefsky 2012).

First evidence that inflammatory processes might be involved in the regulation of insulin resistance derived from studies in patients with sepsis and septic shock (Clowes et al. 1978; Raymond et al. 1981). One of the initial observations especially suggested that insulin resistance takes place in skeletal muscle (Raymond et al. 1981).

Insulin resistance has been observed and described in many chronic inflammatory/immune-mediated diseases over the years (Svenson et al. 1987). In support of a link between insulin resistance and inflammatory pathways, a recent study of experimental endotoxemia demonstrated that in humans acute inflammation induced by endotoxin administration induces systemic insulin resistance, and more importantly suppressed insulin receptor substrate (IRS1) and markedly induced suppressor-of-cytokine-signaling proteins in adipose tissue accompanied by increased tissue expression of pro-inflammatory cytokines (Mehta et al. 2010) further supporting the notion that systemic inflammation indeed affects insulin sensitivity. One of the first and most important observations that indeed inflammatory cytokines might be relevant in obesity and associated insulin resistance came from a study by Hotamisligil et al. (1993). At that time tumor necrosis factor (TNF)-α was considered a cytokine mainly associated with inflammation and cachexia and therefore it was especially challenging to convince the scientific community that this cytokine is overexpressed in adipose tissue and might play a role in metabolic disorders. Therefore, this publication must nowadays be considered as the beginning of the current paradigm that inflammation might drive insulin resistance as Hotamisligil et al. (1993) showed that neutralization of TNF-α improved glucose metabolism in different animal models of obesity and diabetes. Clinical observations underpinning such an association followed a few years later. Studying C-reactive protein levels in "healthy" subjects suggested a correlation with obesity and insulin resistance, thereby for the first time demonstrating that indeed chronic inflammation might take place in these conditions (Hak et al. 1999; Yudkin et al. 1999). These landmark clinical studies strengthened the association between low-grade inflammation, atherosclerosis, obesity and insulin resistance strongly implicating that inflammation could be critically involved in the pathophysiology of insulin resistance. Importantly, however, only interventional therapeutic studies targeting key pro-inflammatory cytokines will and would be able to definitely prove that besides all fascinating preclinical evidence the association of inflammation and insulin resistance is also relevant in humans. In this article, we will summarize the current information of targeting the key pro-inflammatory cytokines TNF-α, interleukin (IL)-1 or IL-6 in humans and effects on glucose metabolism and insulin resistance.

TNF-α: the Prototypic "Metabolic" Cytokine?

As stated, TNF-α had been the first pro-inflammatory cytokine being associated with obesity and related insulin resistance (Hotamisligil et al. 1993). Further evidence supporting a key role for TNF-α in insulin resistance came from studies where they observed that mice lacking TNF-α or TNF receptors had improved insulin sensitivity in both dietary and genetic (*ob/ob)* models of obesity (Uysal et al. 1997). Supportive and similar observations were made in humans (Kern et al. 1995) with increased adipose tissue TNF-α expression in obesity and improvement of this increased TNF-α expression following weight loss (Dandona et al. 1998; Moschen et al. 2010). Initial studies suggested that the defect in insulin signaling could be attributed to serine phosphorylation of IRS1 at serine-307 residue by activation of jun-*N*-terminal kinase 1 (JNK1), providing a first explanation how inflammation and insulin resistance might be linked (Aguirre et al. 2000; Hotamisligil et al. 1996). At a molecular level, stimulation of cells with TNF-α or increased concentrations of free fatty acids inhibited phosphorylation of serine residues of IRS1 (Aguirre et al. 2000). Therefore, all these studies evaluating the role of TNF-α in inflammation, insulin resistance and obesity paved the way for later studies with other pro-inflammatory cytokines. TNF-α can nowadays be considered as "the" pro-inflammatory cytokine which introduced the link between inflammation, obesity and insulin resistance.

In searching for underlying mechanisms, researchers studied various signaling pathways and transcription factors and Yuan et al. (2001) identified the IKKβ pathway as a target for TNF-α-induced insulin resistance. Two other studies had also demonstrated the relationship between IKKβ expression in the liver and insulin resistance (Arkan et al. 2005; Cai et al. 2005). Other transcription factors and kinases such as JNK1 and 2 have also been shown to be crucially involved at least in animal models in metabolic dysfunction (Samuel and Shulman 2012). Not surprisingly, enhanced tissue expression of a pro-inflammatory cytokine such as TNF-α in the adipose tissue is associated with an increased recruitment of activated macrophages (adipose tissue macrophages: ATMs). These ATMs are recruited via chemokine signaling and most chemokines are expressed under the control of a pro-inflammatory cytokine. Chemokine ligand CCL2 (also named monocyte chemoattractant protein 1) had been one of the first chemokines demonstrated to be highly expressed in the adipose tissue of obese animals and humans (Weisberg et al. 2003). This seems relevant as deletion of CCL2 in animals results in improved insulin resistance and resulted in a decrease of liver fat content after a high-fat diet (Kanda et al. 2006). Also deletion of its receptor, the C–C motif chemokine receptor 2 reduced ATM infiltration and resulted in metabolic improvement (Weisberg et al. 2006). All these chemokine studies, though focusing on preclinical models proved that these molecules influence the appearance of ATMs in adipose tissue in case of obesity

and related inflammation and targeting these pathways improves insulin resistance and metabolic balance. These studies also raised hope that blockage of pro-inflammatory cytokines could be of clinical benefit in obesity-related inflammation.

So what about clinical experience of neutralizing TNF-α in metabolic inflammation?

Infliximab, a potent TNF-α-neutralizing monoclonal antibody used in the treatment of many chronic inflammatory disorders, has been demonstrated to improve steatosis and insulin signaling in a genetic mouse and rat model of high-fat diet-induced insulin resistance, suggesting that neutralization of this key cytokine not only improved liver inflammation/steatosis/fibrosis but also insulin signaling (Barbuio et al. 2007; Li et al. 2003). A first study in 27 patients with rheumatoid arthritis undergoing infliximab therapy showed a rapid beneficial effect on insulin resistance and insulin sensitivity (Gonzalez-Gay et al. 2006). Other studies, however, using neutralizing anti-TNF antibodies in humans did not show an improvement in insulin sensitivity (Bernstein et al. 2006; Ofei et al. 1996). Also single doses of TNF-α antagonists failed, although not unexpectedly, to improve insulin resistance in diabetic or obese subjects (Ofei et al. 1996; Paquot et al. 2000). In addition, subsequent placebo-controlled studies conducted over a treatment period of 4 weeks provided no improvements in insulin sensitivity either in obese, diabetic subjects (Dominguez et al. 2005) or in obese, insulin-resistant subjects without diabetes (Bernstein et al. 2006). Another study assessed the effect of adalimumab on insulin resistance in rheumatoid arthritis patients. These patients with active disease showed impaired insulin resistance which remained unaffected by anti-TNF therapy despite a reduction in systemic inflammation (Rosenvinge et al. 2007). A study from Spain investigating 16 patients with rheumatoid arthritis also failed to show any benefit on insulin resistance, adiposity distribution, and serum levels of most adipocytokines by long-term use of anti-TNF agents (Ferraz-Amaro et al. 2011) raising again doubts on the usefulness of anti-TNF agents in insulin resistance. Wascher and colleagues assessed nine "healthy" obese but insulin-resistant men by treatment with infliximab at weeks 0, 2 and 6 (Wascher et al. 2011). In this carefully performed study the authors failed to demonstrate any beneficial effect of infliximab on insulin resistance by assessing not only homeostasis model assessment (HOMA) index, but also performing intravenous glucose tolerance testing. This study therefore also seriously doubts the clinical relevance of TNF-α in obesity-related insulin resistance. TNF-α inhibition also seems not to alter insulin resistance in patients with inflammatory bowel diseases (Koutroubakis et al. 2009). Also other clinical studies failed to demonstrate an effect of anti-TNF therapy on glycemic control (da Silva et al. 2010). In this report, 62 normoglycemic patients with ankylosing spondylitis, psoriatic arthritis or juvenile idiopathic arthritis were studied.

After two decades of evidence that adipose tissue in case of obesity is crucially associated with increased TNF-α expression, after more than one decade use of anti-TNF agents in various situations associated with insulin resistance, it appears unlikely that this increased expression reflects an attractive therapeutic target. On the other side, there is no doubt that low-grade chronic inflammation is part of obesity and related insulin resistance but probably other pro-inflammatory cytokine are of more relevance. Thus, TNF-α blockade appears to have no efficacy on insulin resistance in humans.

IL-1: Initially Neglected but Full of "Therapeutic Hope"?

The pro-inflammatory IL-1 family members IL-1α and IL-1β were among the first identified cytokines (Dinarello 2011). Considerable evidence has been generated in the last years that IL-1 family (IL-1F) of cytokines might also play an important role in metabolic inflammation (Donath and Shoelson 2011; Stienstra et al. 2012). Several IL-1F cytokine members are produced by human adipose tissue in case of obesity including the pro-inflammatory IL-1α, IL-1β or IL-18 and the anti-inflammatory proponents IL-1 receptor antagonist (IL-1Ra) or IL-37 (Moschen et al. 2011; Nold et al. 2010). IL-1β induces insulin resistance in both differentiating and differentiated cultured adipocytes and its expression was upregulated in adipose tissue of obese and insulin-resistant mouse models (Lagathu et al. 2006). IL-1β is able similar to other pro-inflammatory stimuli to reduce IRS1 expression at a transcriptional level through an ERK-dependent mechanism (He et al. 2006). Both IL-1α and IL-1β-deficient mice are almost entirely protected from liver inflammation after diet-induced steatosis suggesting that these pro-inflammatory IL-1 cytokines might be crucially involved in the development of liver inflammation (Kamari et al. 2011). The results presented in the Kamari study are in accordance with another recent report where authors observed that TLR9 controls steatohepatitis in a diet-induced model of obesity via IL-1β (Miura et al. 2010).

IL-1Ra is markedly upregulated in the serum of obese patients, is correlated with body mass index and insulin resistance, and is overexpressed in the white adipose tissue of obese humans (Meier et al. 2002; Pihlajamaki et al. 2012). In one of these studies, Meier et al. (2002) observed that obesity is associated with a more than fivefold increase in circulating IL-1Ra levels and weight loss induced by gastric bypass surgery resulted in a decrease in circulating

IL-1Ra levels after 6 months. It has been recently shown that elevated IL-1Ra levels persist over more than 10 years and at an accelerated rate in the last 6 years before T2D diagnosis (Carstensen et al. 2010). We recently investigated the effect of excessive weight loss on subcutaneous adipose tissue and liver expression of several IL-1F members such as IL-1α, IL-1β, IL-18, IL-1Ra, and IL-37 (Moschen et al. 2011). Especially subcutaneous adipose tissue mRNA expression of IL-1β decreased significantly after extensive weight loss, whereas expression of the anti-inflammatory cytokine IL-37 increased. Improvements in systemic inflammatory parameters after weight loss may therefore be explained partly by changes in adipose tissue cytokine expression profiles.

A remarkable study in Goto-Kakizaki rats demonstrated that increased pancreatic IL-1β activity promotes cytokine and chemokine expression resulting in activation and recruitment of innate immune cells (Ehses et al. 2009). This activity was associated with pancreatic inflammation, β-cell functional mass and insulin sensitivity and more importantly IL-1 neutralization by IL-1Ra improved hyperglycemia and insulin sensitivity (Ehses et al. 2009). The most convincing data that IL-1-type of family cytokines are involved in insulin resistance and diabetes came from human studies were Donath and colleagues convincingly demonstrated that neutralization of IL-1 by IL-1Ra improved hyperglycemia and glycemic control strongly supporting a role for IL-1 in diabetes and related insulin resistance (Larsen et al. 2007, 2009). In the latter report, Larsen et al. (2009) found that IL-1 neutralization with IL-1Ra (anakinra) resulted in improvement of systemic inflammation lasting 39 weeks after treatment withdrawal suggesting indeed a very sustainable effect by IL-1 neutralization. IL-1β-mediated toxicity seems to play a major role in T2DM and insulin resistance suggesting that inflammation contributes in a major fashion to these pathologies (Donath and Shoelson 2011). Indeed, XOMA 052, an anti-IL-1β monoclonal antibody improves hyperglycemia and pancreatic β-cell function in animal models of obesity and insulin resistance (Owyang et al. 2010). In these studies, IL-1β neutralization improved β-cell apoptosis, increased its proliferation and finally led to β-cell sparing accompanied by increased insulin sensitivity. Based on these and various other preclinical studies a large study has been investigated (CANTOS study, Canakinumab Anti-Inflammatory Thrombosis Outcome Study), where it remains to be proven whether IL-1 neutralization by a monoclonal antibody against IL-1β is effective in reducing rates of recurrent myocardial infarction, stroke, cardiovascular death and T2D among stable patients with coronary disease (Ridker et al. 2011). This study will definitely prove whether IL-1β is of clinical relevance in metabolic inflammation, and atherosclerosis. Overall, these studies together convincingly show that IL-1F members are important mediators in metabolic inflammation. Therefore, it seems currently that neutralization of IL-1 is more promising than neutralizing other pro-inflammatory cytokines in insulin resistance and metabolic inflammation.

IL-6: the "Confusing" Cytokine in Insulin Resistance

IL-6, one of the first identified pro-inflammatory cytokines and crucially being involved in the regulation of the acute phase response, was among the first cytokines being discussed as a marker of insulin resistance and cardiovascular disease. Serum concentrations of IL-6 decreased in parallel with weight loss and improvement of insulin resistance in patients undergoing bariatric surgery (Kopp et al. 2003) and subcutaneous and visceral fat has been demonstrated as an important site for IL-6 secretion in humans (Moschen et al. 2010). This cytokine could be indeed involved in the pathogenesis of hepatic insulin resistance as insulin sensitivity increases in diet-induced obese mice treated with anti-IL-6 antibodies (Klover et al. 2005). The role of IL-6 in experimental animals and associated insulin resistance remained controversial over the years. IL-$6^{-/-}$ mice were characterized as insulin resistant and developed mature-onset obesity (Wallenius et al. 2002). However, these results were not reproducible in another IL-$6^{-/-}$ mouse model as these authors did not observe age-related obesity (Di Gregorio et al. 2004). The "IL-6 puzzle" seems to continue as a recent study observed that this pro-inflammatory cytokine enhances insulin secretion by inducing release of glucagon-like peptide-1 from intestinal L cells and pancreatic α cells (Ellingsgaard et al. 2011). A single bolus injection of IL-6 to mice significantly increased glucose-stimulated insulin secretion in mice fed chow, a high-fat diet, in *ob/ob* and *db/db* mice. Interestingly, in a high-fat diet model with β-cell destruction by streptozotocin, IL-6 failed to enhance insulin secretion. When *db/db* mice received for 4 weeks an anti-IL-6 antibody the authors observed a deterioration of glucose tolerance without any effects on insulin tolerance. The authors concluded that this entero-endocrine-islet axis mediated by IL-6 might allow for adaptation to increased insulin demand during obesity and failure to adapt may promote T2D. Such a role for IL-6 is questioned in humans by two recently published although rather small clinical trials. One study assessed the influence of tocilizumab, an anti-IL-6 antibody used in the treatment of rheumatoid arthritis (Ogata et al. 2011). In this study, 39 patients with active rheumatoid arthritis were followed for 6 months and 10/39 study patients were diabetic. Anti-IL-6 therapy resulted in a significant drop of HbA1c within 4 weeks, a time period where accompanied corticosteroid therapy was not

modified. A further decrease was observed in the next five treatment months, probably also influenced by tapering of corticosteroids. Nevertheless, this observation is interesting as it suggests that neutralization of IL-6 in humans could improve hyperglycemia. A similar observation has been made by Schultz et al. (2010). In this small study including 11 non-diabetic patients a 3-month therapy again with tocilizumab decreased HOMA index significantly and improved insulin sensitivity. Interestingly, a recent study suggested also that on the basis of genetic evidence in human beings IL-6R signaling seems to have a causal role in development of coronary heart disease, a condition commonly associated with low-grade inflammation and insulin resistance (Hingorani and Casas 2012). To summarize, preclinical data currently do not allow a convincing assumption whether IL-6 is beneficial or detrimental in the control of hyperglycemia. Studies in both directions have been presented in the last years. At least two small clinical trials, however, suggest a beneficial effect and we are eager to see more clinical data on the use of tocilizumab in patients with insulin resistance and/or T2D. Overall, it should be mentioned that anti-IL-1 therapies strongly decrease IL-6 levels and therefore it remains to be established whether neutralizing this cytokine would be more effective than neutralization of IL-1.

Other Anti-Inflammatory Strategies to Overcome Insulin Resistance

Yin et al. (1998) had demonstrated in an earlier report that aspirin and salicylates were able to inhibit the activity of IKKβ. The concept of "inflammation in diabetes" had been suggested by a clinical study reported more than 135 years ago by Ebstein (1876), where he showed that high doses of salicylates lowered high blood glucose concentrations. Yuan et al. (2001) demonstrated in their work that high doses of salicylates reversed hyperglycemia, hyperinsulinemia, and dyslipidemia in *fa/fa* rats and *ob/ob* mice, and overexpression of IKKβ attenuated insulin signaling in cultured cells. A recent clinical study demonstrated that high-dose aspirin (up to 7 g/day) improves glucose tolerance and triglyceride levels (Hundal et al. 2002). These positive effects of high-dose aspirin on insulin resistance are, however, limited by its toxicity profile, especially in the gastrointestinal tract. Nonacetylated salicylates with less side effects such as salsalate, a nonacetylated prodrug of salicylate, also inhibit nuclear factor-κB through direct inhibition of IKKβ (Yin et al. 1998). Indeed, salsalate has been studied in patients with T2D (Goldfine et al. 2010). The authors investigated the efficacy and safety of salsalate at different doses in patients with T2D. Patients received placebo or salsalate in dosages of 3.0, 3.5, or 4.0 g/day for 14 weeks parallel to their current therapy. Higher numbers of patients in the three salsalate treatment groups experienced decreases in HbA1c levels. In a recently presented larger randomized controlled trial, 286 patients with T2D received 3.5 g of salsalate or placebo daily for 48 weeks (Goldfine et al. 2012). Over the study period, salsalate reduced HbA1c levels significantly by 0.24 % and 87 % of study patients receiving placebo required an increase in their diabetes medication, whereas 62 % of patients treated with salsalate could reduce their medication. These studies have been a major first hint that an anti-inflammatory treatment approach seems promising in the treatment of T2D and that inflammation could be indeed a valid pharmaceutical target in the treatment of this disease.

Another question remains whether aspirin could be preventive for the development of T2D. For this reason, women were randomly assigned to receive aspirin ($n = 19.326$) or placebo ($n = 19.390$), without statistically significant difference in the incidence of T2D at treatment start were followed for more than 10 years. There were 849 cases of diabetes in the aspirin group and 847 in the placebo group suggesting that long-term low-dose aspirin does not prevent the development of T2D in initially healthy women (Pradhan et al. 2009). Therefore, higher doses might be needed to exert anti-inflammatory and anti-diabetic effects. Nonacetylated salicylates such as salsalate have so far not been studied in the preventive setting.

Conclusions

It became evident in the last two decades that inflammatory pathways are critically involved in the pathogenesis of insulin resistance. This intriguing concept is also supported by many clinical observations in patients with T2D and NAFLD, where insulin resistance is correlated with a state of low-grade chronic inflammation. Based on mainly preclinical findings clinicians have tried to find out whether certain anti-cytokine strategies in humans are able to revert insulin resistance or improve metabolic control in T2D. Whereas TNF neutralization in humans seems to have no effect on hypergylcemia thereby doubting a relevant role for this cytokine in metabolic inflammation, neutralization of IL-1 and/or IL-6 currently seems more promising. Larger and prospective trials are needed to finally prove if the fascinating results obtained mainly in preclinical animal studies hold their promise also in "human reality". Nevertheless, current data are sufficient to claim a role for inflammatory pathways in the pathophysiology of insulin resistance not only in preclinical models, but also in humans.

Acknowledgments This work was supported by the Christian Doppler Society.

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