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IL-1 family members in the pathogenesis and treatment of metabolic disease: Focus on adipose tissue inflammation and insulin resistance

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Abstract

Obesity is characterized by a chronic, low-grade inflammation that contributes to the development of insulin resistance and type 2 diabetes. Cytokines and chemokines produced by immunocompetent cells influence local as well as systemic inflammation and are therefore critical contributors to the pathogenesis of type 2 diabetes. Hence, cytokines that modulate inflammatory responses are emerging as potential targets for intervention and treatment of the metabolic consequences of obesity. The interleukin-1 (IL-1) family of cytokines and receptors are key mediators of innate inflammatory responses and exhibit both pro- and anti-inflammatory functions. During the last decades, mechanistic insights into how the IL-1 family affects the initiation and progression of obesity-induced insulin resistance have increased significantly. Here, we review the current knowledge and understanding, with emphasis on the therapeutic potential of individual members of the IL-1 family of cytokines for improving insulin sensitivity in patients with diabetes.

Keywords

Interleukin-1 family; obesity; inflammation; insulin resistance; adipose tissue

Historical Context

Worldwide the incidence of obesity has increased dramatically. In 2013, the global proportion of overweight (defined as a Body Mass Index (BMI) above 25 kg/m^2) or obese (BMI above 30 kg/m^2) adults was estimated at 37.5% [1] Obesity is one of the main

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contributors for the development of insulin resistance, and strongly increases the risk for type 2 diabetes. Inflammatory mediators link obesity to insulin resistance [2]. Obesity itself results in a pro-inflammatory state in metabolic tissues, as illustrated by the upregulation of pro-inflammatory cytokines, such as Interleukin (IL)-1β and TNFα, which can directly interfere with insulin signaling in adipocytes, hepatocytes, fibroblasts and myocytes [3-10].

The first observation revealing upregulation of TNFα in obese adipose tissue [11] that contributed to the development of insulin resistance [6], evoked interest in the role of inflammation during obesity. In 2003, it was reported that macrophages infiltrate adipose tissue in obesity [12, 13]. These cells produce pro-inflammatory cytokines, such as IL-1β, TNFα, IL-6 and MCP-1 that contribute to the pathogenesis of obesity-induced insulin resistance. Since that publication, the number of studies investigating specific inflammatory processes in adipose tissue during the development of obesity and related diseases has increased dramatically. Reports reveal that both adaptive and innate immune responses contribute to the onset and progression of obesity-induced adipose tissue inflammation [14, 15].

Importantly, cytokines of the IL-1 family are critical regulators of innate immune responses. This family of cytokines comprises both pro- and anti-inflammatory members. IL-1α and IL-1β are classic pro-inflammatory cytokines; both are antagonized by the natural occurring IL-1 receptor antagonist (IL-1Ra), also a member of the IL-1 family. IL-18, another member of the IL-1 cytokine family, is generally considered a pro-inflammatory cytokine [16]. At the beginning of this millennium, 7 other members of the IL-1 family have been identified. Of these novel members, IL-33, IL-36α, IL-36β and IL-36γ are generally described as pro-inflammatory cytokines that contribute to inflammatory responses [17-19]. In contrast, IL-37 is an anti-inflammatory cytokine [20], similar to IL-36 Receptor antagonist (IL-36Ra) that specifically blocks IL-36 signaling [19]. The role of IL-38, also ascribed with receptor antagonizing properties, appears to have anti-inflammatory properties largely unknown [21, 22].

Growing interest in the role of IL-1 signaling was present after the observation that circulating IL-18 and IL-1Ra levels were increased in obese subjects and patients with type 2 diabetes, respectively [23, 24], and that adipose tissue is a major source of circulating IL-1Ra levels [25] (Figure 1). Early studies from the 1980s had already demonstrated that IL-1β selectively damages the insulin-producing beta cells in the pancreatic islets of Langerhans [26, 27], suppresses food intake [28] and activates energy metabolism [29]. In 2002 the importance of the role of IL-1β was highlighted by the observation that hyperglycemia, characteristic for type 2 diabetes, increased IL-1β production from the β-cells themselves leading to impaired β-cell function and reduced insulin production [30].

In 2006, a causal relation between an IL-1 family member and insulin sensitivity was established in mice, as deficiency of IL-18 in mice appeared to induce hyperphagia, obesity and insulin resistance [31]. Since then, several studies have focused on deciphering the contribution of IL-1 family members to the progression of obesity-induced inflammation and the development of insulin resistance. So far, nearly all cytokines of the IL-1 family have been linked to obesity. Importantly, and in contrast to the pro-inflammatory properties

of the family, also insulin-sensitizing effects of anti-inflammatory family members have been described in obesity. This review addresses the emerging role of the IL-1 family members in metabolic inflammation and insulin resistance, with a specific focus on adipose tissue. In addition, the current and future therapeutic applications of cytokine blocking strategies as well as the use of anti-inflammatory cytokines from the IL-1 family to enhance insulin sensitivity will be presented.

IL-1α, IL-1β and IL-1 Receptor antagonist

IL-1 is a master regulator of innate immune responses by controlling numerous inflammatory processes [32]. 30 Years ago, two distinct forms of IL-1 were cloned [33, 34] and termed IL-1α and IL-1β [35]. Both IL-1α and IL-1β interact with the IL-1 receptor 1 (IL-1R1) and recruit the IL-1 receptor accessory protein (IL-1R3, formerly IL-1RAcP) to induce a downstream signal via several inflammatory kinases, such as Myd88, ERK, JNK and NFκB, leading to transcription of inflammatory, catabolic genes [36-38]. Importantly, these signaling molecules overlap in that the IL-1 Receptor 1 (IL-1R1) and Tolllike receptors share the same signaling domain termed Toll-IL-Receptor (TIR) [39]. IL-1Ra on the other hand has anti-inflammatory effects by binding to the IL-1R1 and specifically inhibiting IL-1 signaling [40]. Endogenous IL-1Ra is increased during inflammation to oppose IL-1 signaling. Together, IL-1α, IL-1β and IL-1Ra are the most studied members of the IL-1 family and their respective biological activities are pivotal for inflammatory mechanisms in disease [41]. Indeed, IL-1 activity is linked to several auto-inflammatory diseases, including atherosclerosis and gout [42, 43].

There are considerable differences in the localization, regulation and function of IL-1α and IL-1β. First, whereas the IL-1β precursor is produced by innate immune cells (i.e. monocytes, macrophages and dendritic cells), the IL-1α precursor is constitutively expressed in resting cells in health [36]. Secondly, intracellular processing of the IL-1β precursor is tightly controlled by inflammatory stimuli such as LPS, IL-1α and IL-1β [44]. This results in IL-1β precursor activation by caspase-1, which, in turn, is activated by inflammasomes [45]. In contrast, extracellular activation of the IL-1β precursor by other serine proteases (*i.e.* proteinase-3, elastase and cathepsin G) [46] is less tightly controlled and more dependent on presence of neutrophils. The precursor of IL-1α on the other hand is present as a biologically active form. The IL-1α precursor can be cleaved by calpain, and the biological function of the processed protein appears to be more active than the precursor. The IL-1α precursor is released from necrotic cells and as such, may act as an alarmin, a signal released from dying cells that initiates an inflammatory response via IL-1R1 [36]. Moreover, IL-1α is a dual-function cytokine, since the cytokine translocates to the nucleus as a pro-inflammatory transcription factor for genes, such as IL-1, IL-6 and IL-8 [32].

IL-1α, IL-1β and IL-1Rα in obesity and insulin resistance in humans

Evidence reveals that IL-1 activity is of importance in the pathology of type 2 diabetes by mediating obesity-induced inflammation and directly aggravating insulin resistance. In addition, IL-1β contributes to the development of type 2 diabetes by inhibiting β-cell function and destroying β-cell mass, as reviewed elsewhere [47-50].

30 Years ago, IL-1 was reported to act as an anorexia-inducing cytokine during host responses to infection [28]. Indeed, known as the fever-inducing cytokine, IL-1 was shown to inhibit food intake [28] and stimulated resting energy expenditure during febrile conditions [29]. Thus, besides induction of inflammation and fever, IL-1 also affected metabolic pathways during infections. Only two decades later, the first relations between IL-1 and obesity were revealed. In obesity, peripheral blood mononuclear cells (PBMCs) showed increased IL-1α production *ex vivo* [51] and elevated plasma levels of IL-1α and IL-1β were found [52, 53]. Notably, circulating levels of IL-1α, IL-1β, and antiinflammatory IL-1Ra were all positively correlated with obesity [24, 53].

Combined with the observation that adipose tissue appeared to be a major source of IL-1Ra production [25], the data prompted a considerable interest into the role of IL-1 in the development of obesity-induced inflammation and insulin resistance. More detailed analysis of adipose tissue revealed that human visceral adipose tissue (VAT), considered to be a major contributor to the increased levels of circulating inflammatory cytokines as well as the development of insulin resistance during obesity, contains higher levels of IL-1α, IL-1β and IL-1Ra as compared to subcutaneous adipose tissue (SAT) [54, 55]. Moreover, the inflammasome components NLRP3 and ASC, as well as caspase-1 were more active and more abundant in VAT compared to SAT, resulting in enhanced IL-1β processing and release [54]. Notably, whereas the cellular origin of IL-1β and IL-1Ra is found within the stromal vascular fraction (SVF) of the adipose tissue [56], the upstream IL-1β activator caspase-1 is especially expressed in the adipocyte fraction [57]. This finding strengthens the hypothesis that cross-talk between products of resident macrophages and products of adipocytes affect each other and therefore may determine the net inflammatory trait of the adipose tissue and its output function [58]

In adipose tissue (VAT & SAT) of obese as compared to lean individuals, mRNA and protein levels of IL-1β and IL-1Ra are increased [59, 60]. Moreover, weight loss markedly reduces mRNA expression of IL-1β in adipose tissue [55, 61], suggesting that bodyweight or fat mass is a significant determinant for secretion of IL-1β by adipose tissue. In addition, augmented activity of the NLRP3 inflammasome and IL-1β in adipose tissue seems to distinguish metabolically unhealthy obese individuals (*i.e.* having several components of the metabolic syndrome), from metabolically healthy obese individuals [59].

Contributions of IL-1β and IL-1Rα to the development of obesity and insulin resistance

Noticeably, until the beginning of the current millennium, the existence of causality between IL-1β and development of type 2 diabetes in humans was unknown. A prospective study of 27,500 individuals addressed this issue. The investigators found that increased plasma IL-1β as well as IL-6 levels augmented the risk to develop type 2 diabetes within a period of 2.3 years [62].

During the last decade, animal studies have further elucidated the causal role of IL-1 in suppressive metabolic health. In diet- or genetically induced obese mice, caspase-1 activity and protein levels of IL-1β are increased in adipose tissue [57]. Moreover, mice lacking components of the inflammasome, IL-1β or its receptor IL-1R1 are protected from the development of high-fat dietinduced inflammation and insulin resistance [63-65],

emphasizing the pathogenic role of inflammasome-mediated IL-1β activity in the development of metabolic disease. Further support comes from studies revealing that mice deficient for neutrophil elastase, another regulator of IL-1β activity, show reduced adipose tissue inflammation and improvement in insulin sensitivity [66, 67]. Moreover, treatment of obese mice with IL-1Ra and inhibitors of caspase-1 or neutrophil elastase led to an improvement in insulin sensitivity levels [57, 67, 68]. Thus, various mouse models characterized by reduced endogenous IL-1β activity have shown protection from the detrimental effects of obesity on adipose tissue inflammation and insulin resistance. It would be worthwhile to establish whether inhibition of other known regulators of IL-1β activity, such as PR3 and cathepsin G, have similar insulin-sensitizing effects.

In vitro studies have also revealed the pathogenic role of IL-1β in the development of insulin resistance, and the possibilities that IL-1β (signaling) inhibition to enhance insulin sensitivity. Indeed, IL-1β treatment of adipocytes, disturbs insulin signaling via downregulation of insulin receptor substrate-1 expression, leading to a marked reduction of insulin-mediated GLUT-4 translocation [5, 69]. Consistent with this observation, macrophage-derived conditioned medium induces insulin resistance in primary human adipocytes, whereas inhibition of IL-1β signaling using a neutralizing antibody or IL-1Ra reverses this effect [10].

Contributions of IL-1α to the development of obesity and insulin resistance

Although there is ample evidence for the role of IL-1β as a mediator for metabolic inflammation and insulin resistance during obesity, in contrast, the contribution of IL-1α has been less studied. Plasma IL-1α levels were found to be higher in obese mice, yet lower mRNA levels were measured in adipose tissue of obese compared to lean animals [70]. *In vitro*, IL-1α inhibits adipocyte differentiation [70] and reduces insulin signaling in murine adipocytes [71, 72]. *In vivo*, injection of IL-1α in mice increases plasma TG levels [70], but whether IL-1α affects glucose metabolism remains to be determined. Nevertheless, a recent study demonstrated that endogenous oils derived from human adipose tissue activate and recruit neutrophils and macrophages via an IL-1α dependent mechanism [73]. These data suggest that IL-1α may recruit innate immune cells to adipose tissue in response to ‘danger signals' released by necrotic adipocytes. Since (hypertrophic) adipocyte death is increased in adipose tissue during obesity [74], IL-1α may control the initiation of adipose tissue inflammation during obesity.

IL-1 Receptor in the development of obesity and insulin resistance

The concept of causal relationship between increased obesity and increase IL-1β is confounded by the observation that IL-1R1 knockout mice, characterized by absence of IL-1 signaling, paradoxically develop maturity-onset obesity and insulin resistance [75]. Furthermore IL-1Ra knockout mice, characterized by enhanced IL-1 signaling, are resistant to obesity [76]. However, these phenotypes are likely explained by the actions of IL-1 on food consumption and energy expenditure [77]. Suppression of appetite by leptin is dependent on IL-1 and can be reversed by injection of IL-1Ra [78]. This mechanism indicates that basal signaling via the IL-1 receptor is necessary to control central food intake in the brain, and moreover, that a delicate balance between IL-1 and IL-1Ra probably

determines energy balance and glucose homeostasis. The completely disrupted balance in knockout mice could possibly explain the paradoxic phenotypes of increased obesity in the absence of IL-1. Therefore, more subtle modulation of the ratio between IL-1 and IL-1Ra using specific inhibitors may have more relevance for total body physiology and pathology of obesity-induced metabolic disease, as no drug, no antibody and no inhibitor completely prevents IL-1 activity.

Given the large amount of evidence supporting a causal role of IL-1β in the development of adipose tissue inflammation and insulin resistance, there is need to understand the role of IL-1α in obesity, since neutralizing antibodies to IL-1α have been used to reverse the negative nitrogen balance and loss of lean body mass in cancer cachexia as a consequence of metastatic sterile inflammation [79, 80]. Hypothetically, using IL-1α blockade to reverse low-grade inflammation, could restore homeostasis and insulin sensitivity in metabolic inflammation. The governing effects of IL-1α blockade on lean body mass are very interesting with respect to the importance of muscles in metabolic health. Therefore, future studies should study the effects of inhibiting IL-1α in metabolic disease. Tissue distribution, cell type and mechanism for release of both cytokines suggest a different mode of action in low-grade sterile inflammation [81]. Within the context of obesity, IL-1α may be secreted in response to adipocyte cell death or hypoxia, thereby initiating an inflammatory response. Subsequently, the resulting inflammatory signals may induce IL-1β release and activation that further instigates and maintains the inflammatory trait, and inhibit peripheral insulin signaling. IL-1Ra on the other hand, is secreted in parallel to IL-1β and/or IL-1α and therefore related to obesity and insulin resistance. The increased levels of IL-1Ra thus serve as a circulating marker for endogenous IL-1β or IL-1α activity, especially since circulating levels of IL-1Ra are higher and thus easier to measure as compared to IL1p/IL1α. However, in contrast to IL-1β or IL-1α, whether increased IL-1Ra is only a marker for IL-1 activity or intended to reduce IL-1 signaling and thereby dampen the inflammatory response, remains unclear. Nevertheless, administration of IL-1Ra has shown to improve insulin sensitivity in animal models.

Therapy potential of blocking IL-1 signaling

Together, these studies have shown significant mechanistic insights into the contribution of IL-1β in the pathogenesis of obesity-induced insulin resistance. Therefore, inhibition of IL-1β (signaling) itself, or upstream activators of IL-1β activity, such as capase-1, may be an attractive therapeutic target. Indeed, several approaches aimed at modulating IL-1 signaling have been shown to be successful in improving insulin sensitivity in various obese mouse models, as discussed above. In humans, increased IL-1β release can be treated with IL-1 blockade and is successfully applied in patients diagnosed with a broad spectrum of pro-inflammatory diseases [82]. Inhibition of IL-1β actions can be achieved by using neutralizing monoclonal IL-1β antibodies (e.g. gevokizumab or canakinumab). Alternatively, blockade of the IL-1R1 is effective using IL-1Ra (anakinra). Importantly, since this is receptor blockade, anakinra reduces the activities of both IL-1β and IL-1α.

These strategies have been used in several clinical studies to evaluate the therapeutic potential of IL-1β inhibition to improve glycemic control in patients with diabetes, as it was

shown that reducing bioactivity of IL-1 with recombinant IL-1Ra improves β-cell function and reduce glucotoxicity in type 2 diabetes [30]. Indeed, trials revealed that inhibition of IL-1β improves hyperglycemia in type 2 diabetes patients [83-87]. Of note, the reduction in HbA1c levels in these studies was most likely the result of improved β-cell function [85-87], since insulin sensitivity was unaltered in type 2 diabetes patients or subjects with the metabolic syndrome [84, 87, 88]. Thus, although *ex vivo* and *in vivo* studies provide strong evidence that IL-1β is causally involved in obesityinduced insulin resistance, clinical evidence for an improvement of insulin sensitivity upon inhibition of IL-1β is so far lacking. Of note, whereas preclinical studies are performed with genetically identical animals, outcomes of clinical studies may greatly be influenced by genetic variation. For example, circulating levels of IL-1Ra show great inter-individual variation [89]. Possibly, higher levels of IL-1Ra in certain individuals may limit beneficial effects of anti-IL-1β treatment. Conversely, blocking anti-IL-1β in individuals with levels of IL-1 signaling may prove more effective. Therefore, more personalized approaches that include immuno-phenotyping to identify individuals that particularly benefit from anti-inflammatory therapy may improve efficacy of blocking IL-1 signaling in patients with diabetes. Indeed, a more personalized approach is currently being tested in the CANTOS trial that investigates IL-1β inhibition with canakinumab in the prevention of cardiovascular events. The study specifically includes patients with elevated chronic inflammation, as determined by hsCRP levels [90]. Within this large trial, the new onset of type 2 diabetes, determined by insulin sensitivity and β-cell function, will be evaluated as a secondary endpoint [90]. Based on preclinical studies that have been discussed above, new agents aimed at inhibiting upstream regulators of IL-1β production and activity, such as caspase-1 or neutrophil elastase [57, 67] may hold promise.

IL-18

More than 20 years ago IL-18 was identified as gamma interferon (IFN-γ)-inducing factor [91, 92]. IL-18 primarily induces T-helper-1 responses due to the induction of IFNγ in combination with IL-12. However, in the absence of IL-12, there is a role for T-helper-2 [93] and NK-cell maturation, cytokine production and cytotoxicity [92, 94-96]. Similar to IL-1β, the protein is synthesized as an inactive precursor and requires caspase-1 processing for activation [45]. IL-18 binds to the alpha chain of the IL-18 receptor and recruits the IL-18R beta chain, after which it signals through important immune regulatory proteins, such as Myd88, ERK, JNK and NFκB that it shares with IL-1 [97] and Toll-like Receptor signaling [39, 98]. IL-18 forms a complex with the IL-18 Receptor α chain (IL-18Rα) and the IL-18 Receptor β chain (IL-18Rβ) to exert its pro-inflammatory actions. Although IL-18Rα is expressed by most cells, IL-18Rβ is not. IL-18 signaling is therefore dependent on IL-12-induced upregulation of IL-18Rβ. Moreover, IL-18 is inhibited by the natural occurring IL-18 binding protein, which binds free IL-18, but is not a competitor for the IL-18 receptor [99].

Furthermore, IL-18 is strongly associated with development of cardiovascular diseases [100-102], and a causal role for IL-18 in the development of atherosclerosis is supported by numerous experimental animal studies. Overexpressing IL-18 in atherosclerosis prone mouse models increased atherosclerotic plaque development [103-105], while development of atherosclerosis was reduced upon overexpression of IL-18bp [102], or absence of IL-18

[106]. The effects of IL-18 on atherosclerosis are mainly caused by the induction of IFN-γ, an important cytokine in the process of atherogenesis [107].

IL-18 in obesity and insulin resistance in humans

The first studies on the role of IL-18 in obesity and development of type 2 diabetes reported that plasma levels of IL-18 were elevated in obese individuals and subjects with type 2 diabetes [108-111]. Moreover, IL-18 levels were restored in individuals that lost weight after bariatric surgery [112]. Furthermore, several polymorphisms in the IL-18 gene were associated with risk factors for the metabolic syndrome, including increased blood pressure [110], insulin resistance [113, 114] impaired glucose regulation [111], the development of obesity [115] and associated with a higher prevalence of type 2 diabetes [111]. Interestingly, IL-18 was found to be secreted from adipose tissue at a higher rate in obese individuals as compared to lean controls [116, 117]. Moreover, IL-18 is higher expressed in [55] and secreted from [54] visceral as compared to subcutaneous adipose tissue.

Within adipose tissue, IL-18 mRNA is specifically expressed in stromal vascular cells [56, 118]. These observations indicated that increased levels of the pro-inflammatory cytokine IL-18 are associated with an elevated risk to develop metabolic disturbances during obesity. Notably, elevated plasma levels of IL-18 are independent of obesity or type 2 diabetes associated with insulin resistance [119]. Based on these observations, it was thought that elevated plasma levels of IL-18 could possibly play a pathophysiological role in the development of insulin resistance, similar to other pro-inflammatory cytokines. Since clinical studies could not elucidate the causative effects, preclinical experiments in animals were performed [31, 120]. Interestingly, these studies revealed a complex relation between IL-18 and metabolic disease, as discussed below. Of note, as compared to other IL-1 family members, circulating IL-18 plasma levels are substantially higher.

Contributions of IL-18 to the development of obesity and insulin resistance

Studies with IL-18 and IL-18 Receptor knockout mice have shed light on the causal relation between IL-18, obesity and insulin resistance. Similar to humans, obesity increases IL-18 protein levels in adipose tissue from mice, an effect secondary to increased caspase-1 activity [121]. Paradoxically, however, both IL-18 knockout mice and IL-18 Receptor α chain knockout mice display increased bodyweight on normal chow diet and developed insulin resistance [31, 120]. The development of obesity in absence of IL-18 appeared to be due to hyperphagia [31, 120]. Indeed, injection of recombinant IL-18 reduced food intake and bodyweight gain in food deprived WT mice [120]. Together, these studies show that the presence of IL-18 in mice reduces food intake and improves insulin sensitivity. Interestingly, acute injection of recombinant IL-18 in mice directly improves insulin sensitivity, suggesting that the effect of IL-18 on insulin sensitivity is not secondary to a reduction in food intake, but may directly govern insulin signaling [31]. Indeed, others have shown that IL-18 directly improves glucose uptake in murine 3T3 cells *in vitro,* and can counteract the insulin resistance induced by TNFα [122].

The mechanism by which IL-18 enhances insulin sensitivity is unclear. The knowledge that IL-18 signals through STAT3 [31], prompted others to investigate whether IL-18 is able to

activate AMPK, similar to other STAT3 activating proteins [123-125]. Interestingly, administration of IL-18 was shown to activate AMPK in muscle via the IL-18R and overexpression of IL-18 in muscle elicits positive metabolic effects by enhancing lipid oxidation and reducing weight gain in mice [126].

In summary, although increased circulating IL-18 levels are associated with symptoms of the metabolic syndrome and type 2 diabetes in humans, absence of IL-18 has detrimental effects on the development of obesity and insulin resistance in mice. Moreover, IL-18 increases rather than reduces insulin sensitivity *in vivo* and *in vitro,* at least partly via activation of AMPK. Thus, the enhanced IL-18 levels in obese individuals and type 2 diabetes may be more viewed upon as a compensatory response rather than a causal factor in the development of metabolic disturbances. Possibly, circulating IL-18 levels may simply reflect increased inflammasome-mediated caspase-1 activation, which has shown to be detrimental for obesity and insulin resistance, as described above. Alternatively, IL-18 may be secreted as a compensatory response to counteract the state of insulin resistance mediated by other pro-inflammatory cytokines, such as TNFα [122]. IL-18 resistance - the observation of reduced expression of the IL-18 receptor in PBMCs in type 2 diabetes patients [127] -possibly hampers these counteracting effects.

Therapeutic potential of IL-18

In summary, although experimental studies reveal a potential beneficial effect of IL-18 on the development obesity and insulin resistance, studies in human subjects are so far lacking and could be hampered by the presence of IL-18 resistance in type 2 diabetes patients. Importantly, the involvement of IL-18 in atherosclerotic plaque development and in other inflammatory conditions may seriously limit therapeutic options in humans for IL-18 within the context of metabolic disease.

IL-33

IL-33 (formerly IL-1F11), one of the novel IL-1 family members was identified in 2005 [128]. It signals through the ST-2 receptor and its co-receptor IL-1 receptor accessory protein (IL-1RAcP). Several isoforms of the ST2 receptor exist, including a transmembrane receptor (ST2L) and a soluble receptor (sST2), which can serve as a decoy receptor for IL-33 [129]. Full length IL-33 is biologically active, but cleavage by protease elastase, cathepsin G or proteinase 3, results in a 10-fold greater potency to activate ST2 [130, 131]. IL-33 is released by active secretion as well as after cell injury or necrosis, in the latter case acting as an alarmin and activating NF-κB, p38 and JNK [18, 132]. IL-33 is expressed in multiple cells and organs, such as lungs, skin, lymph nodes, adipocytes and myocytes [17, 133]. By inducing T helper type 2 cell polarization and activation [134], IL-33 exacerbates inflammation [135-137]. In the past few years it has emerged as a cytokine playing an important role in several inflammatory diseases [138]: autoimmune diseases [139], rheumatoid arthritis, ulcerative colitis, asthma [140], sepsis [141] and allergy [142]. In addition, it has been ascribed with protective effects in atherosclerosis [143].

IL-33 in humans

The role of IL-33 in obesity, adipose tissue inflammation and insulin resistance has only recently been investigated. Expression of IL-33 was detected in human white adipose tissue as well as in human SGBS (Simpson-Golabi-Behmel-Syndrome) adipocytes and pre-adipocytes *in vitro* [144]. Hypoxia and TNFα, similar to IL-1α and IL-1β present in adipose tissue during obesity, induced IL-33 in SGBS (pre-) adipocytes [144]. Zeyda et al. subsequently observed that expression of IL-33 and its receptor ST-2 in adipose tissue were markedly enhanced in severely obese persons, and demonstrated that the main source for IL-33 in adipose tissue were endothelial cells, not adipocytes [145]. Plasma levels of IL-33 were similar between lean and obese individuals, indicating that in obesity a role for IL-33 may be limited to local effects. A recent study reported even higher IL-33 plasma levels in lean compared to non-lean individuals [146]. Since these observations were done in a relatively small number of individuals, larger studies are needed to further investigate this relationship. Nevertheless, there are reports of IL-33 function as an anti-inflammatory cytokine [18].

IL-33 in the development of obesity and insulin resistance

Similar to the human situation, IL-33 mRNA levels increase in the adipose tissue of diet-induced obese mice compared to WT-mice [145]. Interestingly, genetically obese (db/db) mice that lack leptin receptor signaling do not show an increase of IL-33 mRNA [145]. Notably, IL-33 expression in human adipose tissue significantly correlates with leptin expression [145], suggesting that IL-33 expression may be enhanced by leptin signaling. More evidence for this hypothesis was shown by the observation that leptin increased IL-33 expression in human smooth muscle cells [145]. As leptin levels are increased during obesity, this may be one of the mechanisms underlying the increase in IL-33 in adipose tissue during obesity.

The function of IL-33 in adipose tissue, especially during obesity, is not fully understood. Administration of IL-33 to genetically obese (ob/ob) mice that are leptin deficient reduces adipose tissue weight, fat mass and adipocyte size [147], without effects on total body weight. *In vitro*, recombinant IL-33 reduces adipocyte differentiation and lipid storage in adipocyte cultures. This suggests that IL-33 has potential interesting effects in obesity by reducing lipid storage and adipogenesis.

In addition, IL-33 may influence adipose tissue inflammation during obesity. IL-33 administration to ob/ob mice induces accumulation of T-helper 2 cytokines in serum and adipose tissue [147], which is known to associate with differentiation of macrophages towards an anti-inflammatory M2 phenotype. Indeed, IL-33 enhanced the accumulation of macrophages in adipose tissue, which were mainly the M2 macrophage phenotype. This effect was paralleled by lower fasting glucose levels without changes in insulin levels, suggesting increased insulin sensitivity [147]. Thus IL-33 shows potential as a therapy in obesity to skew adipose tissue macrophages from M1 to M2 phenotype, which may be beneficial for maintenance of insulin sensitivity. Of note, type 2 cytokine signaling has recently been linked to ameliorated adipose tissue inflammation and modulate biogenesis of beige fat [148], suggesting a role for IL-33 in browning of adipose tissue. Interestingly, it

has just been revealed that IL-33 indeed can activate UCP-1 in subcutaneous adipose tissue. Administration of IL-33 increased browning of white adipose tissue in mice and increased energy expenditure [149]. These observations likely explain the earlier observation of a reduced adipose tissue mass upon administration of IL-33 to mice [147]. Together, this shows that recombinant IL-33 may have protective effects concerning adipose tissue mass, adipose tissue inflammation and insulin resistance.

Compared to IL-1 and IL-18, only limited research has been performed concerning the role of IL-33 in metabolic disease. Future research should investigate whether IL-33 has ameliorating effects on insulin, glucose and lipid metabolism in more physiological models of obesity such as HFD-feeding, especially since the current observations are based on recombinant IL-33 treatment in ob/ob mice, which appear to have altered IL-33 signaling (as discussed above). In addition, the effects of recombinant IL-33 on other organs and tissues need to be determined. However, although IL-33 has beneficial effects during obesity, IL-33 as a potential treatment to enhance insulin sensitivity, may be hindered by the pro-inflammatory functions of this cytokine.

IL-37

IL-37 is a unique member of the IL-1 family (formerly IL-1F7). The cytokine broadly inhibits inflammation by reducing several signaling kinases and augmenting anti-inflammation genes [150]. Since 2010, an increasing number of studies have described the anti-inflammatory actions of this cytokine in models of disease [151]. During acute and chronic inflammation, IL-37 shifts the cytokine balance away from inflammation [151]. IL-37 binds to the IL-18 Receptor alpha chain but recruits the orphan IL-1R8 (Formerly, Single Ig IL-1-related Receptor, SIGIRR) rather than the IL-18 Receptor beta chain; thus IL-1R8 functions as the co-receptor for the complex. Despite binding to the IL-18R, IL-37 does not function as an IL-18 receptor antagonist. In fact, low concentrations of recombinant IL-37 are more effective in inhibiting innate inflammation than concentrations 100 fold higher [152], an observation inconsistent with receptor antagonist function. Signaling via IL-1R8 reduces NF-κB and JNK activation, by preventing recruitment of receptor-proximal signaling component MyD88, which transduces signals from IL-1 and IL-18 as well as all TLRs [153, 154]. Since the TIR domain of IL-1R8 is mutated, MyD88 is sequestered to IL-1R8, depriving a proper signal from IL-1 or TLR ligands; as such, IL-1R8 acts as a decoy or sink for MyD88. Thus, IL-1R8 provides the extracellular actions of IL-37 with a mechanism to reduce IL-1 receptor signaling, but also signaling via receptors of the Toll-like receptor family [155].

In addition to an extracellular function, IL-37 has a nuclear function [156]. Similar to IL-1α and IL-33, IL-37 translocates to the nucleus. In contrast to IL-1α and IL-33, IL-37 downregulates the production of pro-inflammatory cytokines [156]. Caspase-1 is necessary for nuclear translocation [157], but appears to play a minor role for the processing and release of IL-37 [157]. Secretion of the IL-37 precursor takes place and provides the extracellular signal [152]. The IL-37 precursor is fully active [158]. Extracellular serine proteases, such as proteinase 3 or elastase, may play a role in processing IL-37 to a more active form.

IL-37 in obesity and insulin resistance in humans

Moschen et al. were the first to show that IL-37 mRNA was present in human adipose tissue [55]. As compared to liver, expression of IL-37 was significantly higher in human adipose tissue, particularly in the visceral fat depot [55]. Within the adipose tissue, the highest levels of IL-37 mRNA were present in the adipocytes, which was in contrast to IL-1β, IL-1Ra, IL-18 and IL-33 that display higher expression levels in the stromal vascular fraction (SVF) [56]. These observations of IL-37 in adipose tissue are compatible with a modulatory role of this anti-inflammatory cytokine in obesity-induced inflammation and insulin resistance. IL-37 mRNA levels in human adipose tissue increase after marked weight loss in morbidly obese individuals [55], and higher IL-37 mRNA levels are associated with markers of enhanced insulin sensitivity and reduced adipose tissue inflammation [56]. No other studies have been performed to investigate the regulation of IL-37 during the development of obesity or type 2 diabetes in humans. In a Chinese cohort, IL-37 plasma levels were elevated in patients with coronary heart disease [159]. It will be interesting to evaluate whether (changes in) tissue or plasma levels of IL-37, or SNPs in the IL-37 gene [160], are associated with a change in the risk to develop metabolic diseases.

IL-37 in the development of obesity and insulin resistance

The causal effects of IL-37 in obesity-related adipose tissue inflammation and insulin sensitivity have been investigated in experimental studies. Since mice do not have a functional IL-37 gene, human IL-37 transgenic mice (IL-37tg) were generated and used for these experiments. High-fat feeding of IL-37tg mice resulted in less adipose tissue inflammation, as determined by a reduced number of adipose tissue macrophages and secretion of pro-inflammatory cytokines, as compared to high-fat feeding of control mice [56]. In addition, IL-37tg mice subjected to 16 weeks of HFD had better glucose tolerance and insulin sensitivity compared to WT mice. In line with these findings, silencing of IL-37 in hepatocytes *in vitro* enhances inflammation and induces insulin resistance. Similar to IL-33, IL-37 not only affects inflammatory pathways, but also directly affects adipogenesis and adiposity. *In vivo*, IL-37tg mice did not develop an obese phenotype in response to HFD-feeding and showed a marked reduction in adipose tissue mass. Moreover *in vitro*, recombinant IL-37 inhibited adipogenesis in human SGBS adipocytes [56]. This suggests that IL-37 exerts direct effects on adipose tissue lipid metabolism, which may be regulated via activation of AMPK. Indeed, IL-37 increases phosphorylation of AMPK in THP-1 cells [150], as well as murine 3T3 adipocytes [56]. AMPK is a central regulator of cellular metabolism [161] and has anti-obesity effects [162]. As AMPK is an important target for healthy metabolism and dampening of inflammation [163], the relation between IL-37 and AMPK provides an interesting target for further investigations.

In summary, the anti-inflammatory and metabolic actions of IL-37, such as activating AMPK and ameliorating insulin signaling, appear to counteract the harmful effects associated with obesity. However, the current studies have limitations and many questions remain. Physiological (human) models are necessary to further understand the role of IL-37 in the metabolic syndrome. It will be necessary to find the (metabolic) stimuli that trigger or suppress IL-37 production. Furthermore, the importance of nuclear versus the extracellular actions of IL-37 in alleviating chronic low-grade inflammation in obesity remains unclear.

Clearly, additional studies are warranted to reveal other biological effects of this cytokine, especially in humans, and to determine whether variation in IL-37 levels (*i.e.* caused by genetic variation) could possibly predict the risk for the development of metabolic diseases.

IL-36α/β/γ, IL-36Ra and IL-38

IL-36 cytokines are new members of the IL-1 family, discovered a decade ago [164-169] and identified as IL-36α, -β, -γ (formerly IL-1F6, -8, -9) and receptor antagonist IL-36Ra (formerly IL-1F5). IL-36α, -β, -γ activate dendritic cells and polarize T-helper cell responses and play a significant role in the pathogenesis of skin diseases. As all pro-inflammatory IL-36 cytokines signal through the same receptor, they elicit similar effects. Thus, differences between these cytokines lie mainly in tissue or cell specific expression and therefore tissue-specific contributions of the various isoforms. The antagonist IL-36Ra blocks the signaling of the three pro-inflammatory IL-36 cytokines [19]. IL-36 cytokines need to be cleaved for full activity [170]. However, unlike IL-1β, proteases other than caspase-1 are likely to be involved with processing of the inactive precursor to an active cytokine [19, 170].

IL-38 (formerly IL-1F10) was first described in 2001 as another novel IL-1 family member [171, 172]. However, the role of IL-38 in human disease is still largely unknown. IL-38 binds to the IL-36 receptor similar to IL-36 receptor antagonist [21]. This suggests that IL-38 may act as an anti-inflammatory cytokine. While other IL-1 family members are acknowledged to play a central role in the development of obesity-induced inflammation and insulin resistance, little is known about the IL-36 and IL-38 cytokines within the development of metabolic diseases.

IL-36 cytokines

Associated with pro-inflammatory effects, it may be expected that IL-36α/β/γ can aggravate metabolic inflammation and that IL-36Ra could balance this, similar to the effects ascribed to the proinflammatory IL-1β and antagonistic actions of IL-1Ra. However, expression of IL-1β and IL-1Ra is abundant in metabolic tissues, such as adipose tissue, whereas for IL-36 cytokines expression is less clear. To date, IL-36α, but not IL-36β, is expressed in adipose tissue [173]. Moreover, expression of IL-36α is relatively higher in the stromal vascular cells as compared to adipocytes. Whether the IL-36 cytokines affect metabolic inflammation or insulin sensitivity has not been evaluated. One report has described the effects of IL-36 cytokines on adipocytes *in vitro* [173]. Hence, both IL-36α and IL-36β induce modest IL-8 production from adipocytes, whereas only IL-36α also induces IL-6 production and reduces adipogenesis. The effect on adipogenesis may be secondary to the induction of IL-6 by IL-36α, since IL-6 is known to inhibit adipogenesis [174]. The difference between IL-36α and IL-36β in this model is remarkable, since both cytokines signal through the same receptor, suggesting that IL-36α may possess a greater ability for induction of specific cytokine secretion. We are not aware of publications that have specifically investigated the role of IL-36γ. Clearly, there is a gap in understand the role of IL-36 cytokines in obesity-induced inflammation and insulin resistance.

IL-38

Whether IL-38 has a role during the development of obesity and related diseases has not been investigated. Nevertheless, a single nucleotide polymorphism (SNP) in the IL-38 gene is associated with plasma C-reactive protein levels [175], a marker that is increased in serum of obese and type 2 diabetes patients. Interestingly, another SNP in a locus close to the IL-38 gene associates with increased circulating IL-1Ra levels [176]. Blocking IL-1β activity with an antibody or with IL-1Ra is promising in treating type 2 diabetes [83, 87, 90]. In line with this, the IL-1Ra-increasing SNP in the IL-38 gene associated with lower fasting insulin levels and HOMA-IR [176]. Other SNPs that were found to associate with elevated IL-1Ra levels were not associated with insulin or HOMA-IR, suggesting that the association of the SNP in IL-38 with metabolic treats is independent of IL-1Ra levels. Clearly, more investigations are needed to elucidate whether IL-38 has any (direct) role in obesity-induced inflammation and type 2 diabetes.

To summarize, the role of the IL-36 subfamily and IL-38 in obesity and metabolic inflammation has not been sufficiently investigated and several questions remain. Is expression of IL-36 cytokines or IL-38 associated with obesity or insulin resistance; are these cytokines present in other metabolic organs, e.g. liver and muscles; are they activated or inhibited during the development obesity; are these cytokines causally involved in obesity-associated adipose tissue inflammation and insulin resistance? Future studies are warranted, before we can understand if there is a role for these members of the IL-1 family in obesity-induced inflammation or development of insulin resistance.

Conclusion

IL-1 family members are major players in the initiation and regulation of inflammation associated with obesity (Table 1). IL-1β is well recognized for its role in insulin resistance during experimental obesity. Therefore, blocking endogenous IL-1 with IL-1Ra counteracts this effect in experimental settings, but can be extended to treatment of clinical insulin resistance with the known limitations, such as safety. However, reducing IL-1 activity to increase insulin sensitivity in human individuals is presently unproven. One advantage of blocking IL-1 is that it directly attacks the upstream inflammation, compared to oral downstream hypoglycemic agents. IL-18 appears to be beneficial for obesity and insulin resistance in animal models, but IL-18 is clearly involved in the pathogenesis of atherosclerosis, which may hamper possibilities as a therapy for metabolic disease. Recently, others and we have shown that IL-33 and IL-37, via anti-inflammatory properties modulate metabolism, and provide possible new targets for future research in combating obesity and type 2 diabetes. Therefore, both blocking pro-inflammatory or increasing (endogenous) anti-inflammatory members of the IL-1 family may be beneficial in metabolic disease. Additionally, ways to identify individuals that may benefit from anti-inflammatory treatment, for example those patients characterized by low endogenous levels of IL-1Ra, may also help to improve treatment outcomes. Other novel members of the IL-1 family (i.e. IL-36α/β/γ, IL-36Ra and IL-38) have not been studied in relation to metabolic diseases so far, but may be interesting cytokines for future research.

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Highlights

- Cytokines of the IL-1 family play an important role in metabolic inflammation
- The development of obesity affects IL-1α, IL-1β, IL-1Ra, IL-18, IL-33 and IL-37 activity
- IL-1α, IL-1β, IL-1Ra, IL-18, IL-33 and IL-37 alter insulin signaling routes
- The IL-1 family of cytokines holds multiple targets to combat metabolic diseases

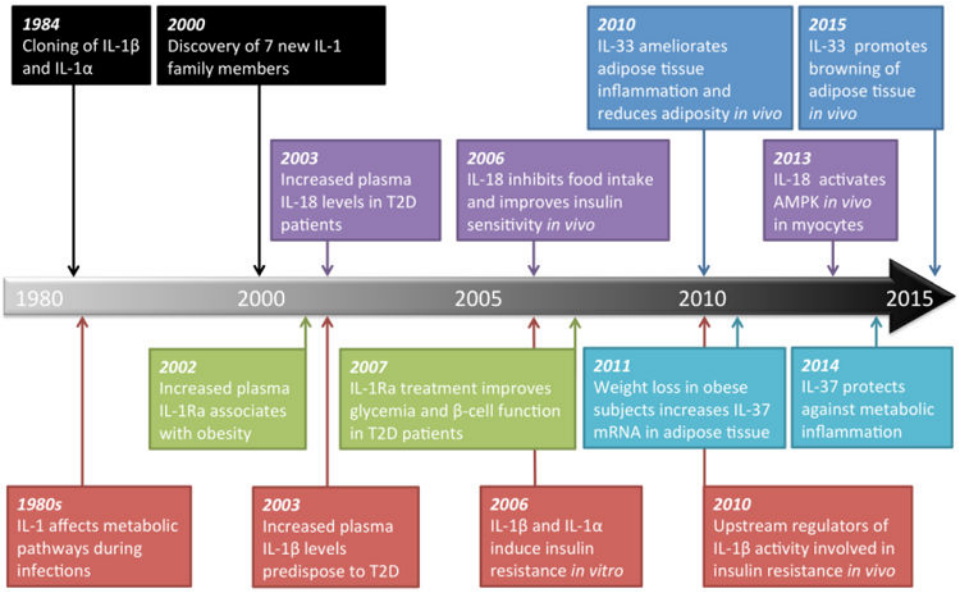

Figure 1.

Timeline of the discovery and specific contribution of IL-1 family members to the development of obesity, inflammation and insulin resistance.

Table 1

Metabolic and inflammatory effects of the IL-1 family of cytokines

Cytokine	Primary Property	Metabolic effects (human)	Metabolic effects (animal)[1]	Mechanism of action
IL-1α	***Pro-inflammatory***	↑ circulating levels in obesity	**↑ plasma TG levels**	Inhibits insulin receptor signalling and induces inflammatory gene transcription
		SNPs associated with obesity and T2D	**↓ insulin sensitivity (*in vitro*)**	
IL-1β	***Pro-inflammatory***	↑ circulating levels augment risk to develop T2D	**↓adipogenesis**	Inhibits insulin receptor signalling and induces inflammatory gene transcription
		SNPs associated with obesity and T2D	**↓insulin sensitivity**	
IL-1Ra	***Antagonist / Anti-inflammatory***	↑ (β-cell function & insulin secretion	***↑insulin sensitivity***	Blocks receptor and prevents IL-1α and IL-1β activities
		↔ insulin sensitivity	**↑ increases appetite**	
		SNPs associated with obesity and T2D		
IL-18	***Pro-inflammatory***	↑ circulating levels in obese, T2D patients	*↓ food intake*	activates AMPK
		levels associate with insulin resistance	*↓ obesity*	reduces food intake
		SNPs associated with obesity and T2D	*↑ insulin sensitivity*	increases atherosclerosis development
IL-33	***Pro-inflammatory***	↔ circulating levels in obese	*↓ adipogenesis*	promotes browning of adipose tissue
			↓ fasting glucose	
IL-37	***Anti-inflammator***	Adipose tissue mRNA associates with enhanced insulin sensitivity	*↓ adipogenesis*	activates AMPK
		↑ mRNA in adipose tissue by weight loss in	*↓ obesity*	
		morbidly obese subjects	*↑ insulin sensitivity*	
IL-36α/β/γ	***Pro-inflammatory***	unknown	unknown	inhibits adipogenesis *in vitro*
IL-36Ra	***Antagonist / Anti-inflammatory***	unknown	unknown	
IL-38	***Antagonist?***	IL-38 SNP associates with	unknown	
		↓ insulin and ↓ HOMA-IR		

Italic fond indicates evidence obtained from knock-out or transgenic models. **Bold fond** indicates evidence obtained from experiments with recombinant molecules.