

Increased IL-1 β activation, the culprit not only for defective insulin secretion but also for insulin resistance?

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Type 2 diabetes is a chronic progressive disease characterized by insufficient insulin secretion to compensate for insulin resistance. The onset of type 2 diabetes and its progression are mainly determined by the progressive failure of the pancreatic islet β -cells to produce sufficient levels of insulin. In contrast, insulin resistance is typically present throughout the progression from prediabetes to the later stages of type 2 diabetes. Increasing evidence associates metabolic disorders, including obesity and type 2 diabetes, with inflammatory processes characterized by elevated production of proinflammatory cytokines and infiltration of immune cells [1]. Recently, three studies were published pointing to a role for the IL-1 β pathway in insulin resistance [2-4]. In the past, the cytokine TNF α has been associated with insulin resistance in liver and fat tissues [5], while IL-1 β was linked to defective insulin secretion in pancreatic islets of type 2 diabetics [6]. In a clinical proof of concept study, attenuation of IL-1 β activity with the receptor antagonist IL-1Ra demonstrated the importance of the innate immune system in glycemic control and identified the pancreatic islet as a prime target for IL-1 intervention [7]. Of note, while

β -cell secretory function improved, changes in peripheral insulin sensitivity were not observed. Similarly, in a recent study with prediabetic patients, IL-1 antagonism improved insulin secretion, but again insulin sensitivity remained unaffected [8]. Using rodent models lacking either the inflammasome component Nalp3, or Pycard, or caspase 1 or its substrate proIL-1 β , the three above-mentioned studies now convincingly show that IL-1 β is also linked to the development of insulin resistance [2-4].

Inflammasomes are danger-sensing multiprotein platforms, which promote auto-catalytic activation of the cysteine-protease caspase 1 required for processing of inactive proIL-1 β into active IL-1 β [9]. Stienstra *et al.* demonstrated that mice lacking caspase 1 or IL-1 β or Nalp3 have improved insulin sensitivity, thereby linking the inflammasomes to insulin resistance [2]. Genetic ablation of inflammasomes not only resulted in increased insulin sensitivity but also regulated adipocyte development and protected from the negative effects of diet-induced obesity. Interestingly, similar to islet β -cells [6], adipocytes themselves produce IL-1 β . This initial event may then lead to IL-1 β -induced chemokines, resulting in the recruitment of macrophages [10-12]. Subsequently, macrophage influx and activation within fat tissue may act as a prominent source

of IL-1 β secretion, triggering insulin resistance. Along this line the papers by B. Vandanmagsar *et al.* [3] and by H. Wen *et al.* [4] take this observation a step further and examine possible mechanisms of inflammasome activation and release of IL-1 β in macrophages during obesity. Both confirm the role of Nalp3 in insulin resistance, but in contrast to the observation by Stienstra *et al.* [2], the protective phenotype was only evident in Nalp3 knockout mice fed a high-fat diet while mice on chow diet did not have improved insulin sensitivity. To gain insight into the mechanism of inflammasome activation in macrophages, both groups used bone marrow-derived macrophages primed *in vitro* with Lipopolysaccharide (LPS). LPS activates Toll like receptor 4 (TLR4) and this priming leads to increased transcription of IL-1 β mRNA. As a second trigger for the LPS-primed macrophages Vandanmagsar *et al.* used ceramides [3], the specific product of long-chain saturated fatty acid metabolism while Wen *et al.* directly used the saturated free fatty acid (FFA) palmitate [4]. Both led to elevated caspase 1 activation and IL-1 β release in macrophages from wild-type mice but not in macrophages from Nalp3 or Pycard knockout mice. Interestingly, Wen *et al.* further show that LPS-palmitate stimulation uses an AMP-activated protein kinase (AMPK)-reactive oxygen species (ROS) pathway to activate the

Nalp3 inflammasome, whereby ROS is derived from mitochondria. Of note, the widely used anti-diabetic drug metformin attenuates AMPK and thus may act via reduction of IL-1 β activity. FFA-mediated IL-1 β formation has also been observed in pancreatic mouse and human islets [13], but unlike in macrophages, FFAs alone are capable to induce IL-1 β release in islets and a further stimulation is observed in the presence of enhanced glucose levels. As elevated glucose concentration defines diabetes, it would be interesting to test whether glucose also promotes IL-1 β release in macrophages or whether this is a path-

way specific for islets that are capable of sensing glucose. Alternatively, high-fat diet was reported to lead to elevated circulating LPS levels [14] and this may prime the inflammasomes in macrophages and render them responsive to elevated FFA levels in prediabetic obese individuals (Figure 1).

As both master cytokines IL-1 β and TNF α are implicated in insulin resistance [2-5], Wen *et al.* used either the receptor antagonist IL-1Ra to block IL-1 activity or an anti-TNF antibody to inhibit TNF and show that they partially reversed the inhibition of insulin signaling mediated by macrophage-condi-

tioned media. Full restoration of insulin signaling was only obtained when IL-1Ra was used in combination with the anti-TNF antibody. Interestingly, the role of IL-1 β in macrophage-mediated insulin resistance is further supported by a reduced ability of Pycard-deficient bone marrow cells to deteriorate glucose tolerance in bone marrow chimera experiments (Wen *et al.*, Figure 8f). This suggests that macrophage influx could indeed mediate insulin resistance via activation of the inflammasomes. A limit to this conclusion is the lack of insulin secretion data to rule out the possibility that the impairment of glucose tolerance

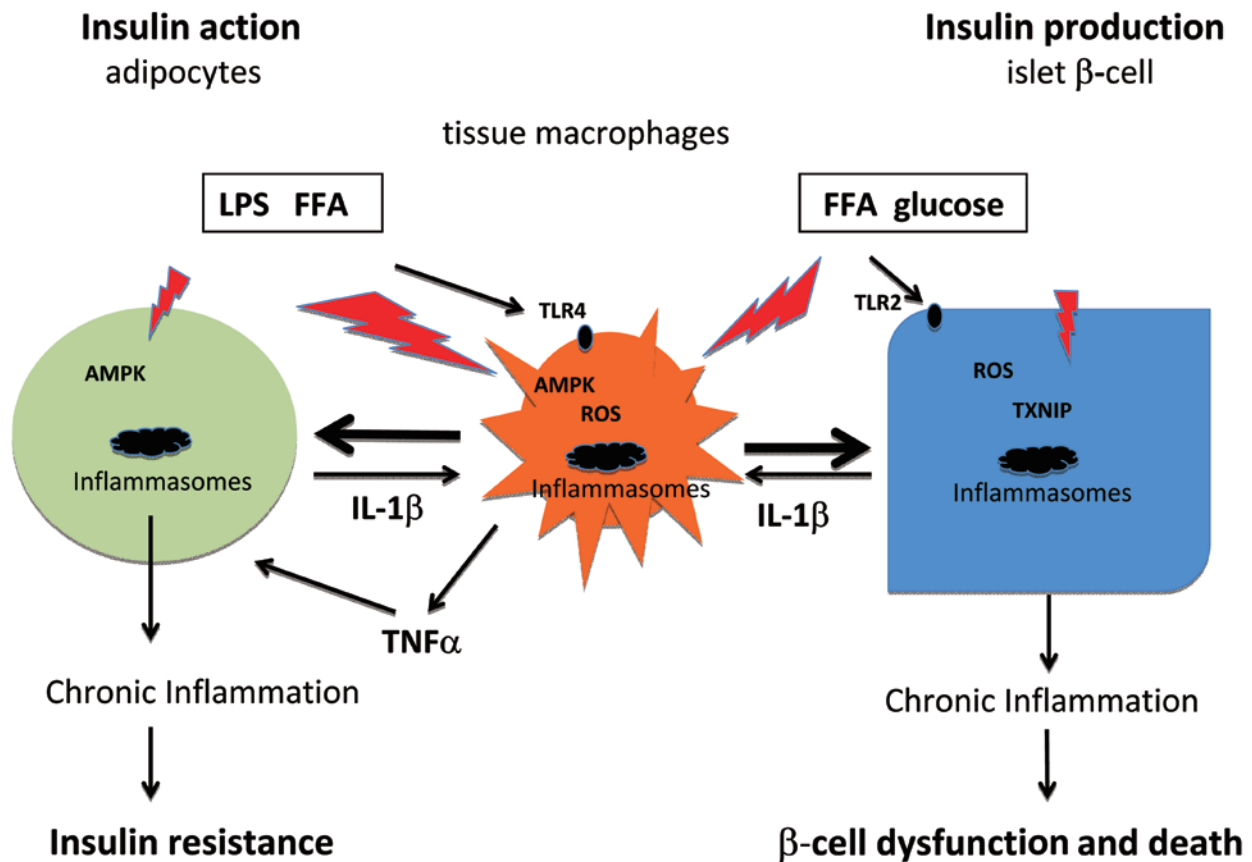


Figure 1 Inflammasome-mediated IL-1 β production impairs glucose homeostasis by inducing insulin resistance and β -cell dysfunction. Metabolic stress activates inflammasomes in islets and in insulin-responsive tissues, leading to the presence of activated macrophages and resulting in an inflammatory state. Two “hits” by LPS and FFA are required in macrophages to activate the inflammasomes via AMPK and subsequent mitochondrial ROS generation. In β -cells FFA and elevated glucose concentrations lead to IL-1 β release, while inflammasomes are activated via glucose-induced dissociation of thioredoxin-interacting protein (TXNIP) from thioredoxin under the influence of ROS. The chronic inflammation in insulin-responsive tissues leads to elevated TNF α and IL-1 β that mediates insulin resistance while IL-1 β in islets impairs the function of the pancreatic β -cell.

by transferred macrophages is due to effects on islet function.

Regardless of the precise underlying mechanism, an impressive number of genetic animal models now demonstrate a role for the inflammasome in mediating IL-1 β -induced insulin resistance. This is further supported by earlier intervention studies showing that IL-1 blockade in animal models of diabetes improved both insulin secretion and sensitivity [15]. This should help to design further clinical studies aiming at improving not only insulin secretion but also insulin action via modulation of the IL-1 β system. Thereby, the sensitivity of the islets to IL-1 β , which express the highest level of IL-1 receptors [13], and possible differences in the pharmacokinetics due to the strong blood flow of the islets have to be taken into account. Thereby, novel long-acting IL-1 β antagonists may be more efficient than IL-1Ra.

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