Cell Metabolism
Perspective

Inflammation in Obesity and Diabetes: Islet Dysfunction and Therapeutic Opportunity

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The role of the immune system is to restore functionality in response to stress. Increasing evidence shows that this function is not limited to insults by infection or injury and plays a role in response to overnutrition. Initially, this metabolic activation of the immune system is a physiological response, but it may become deleterious with time. Therefore, therapeutic interventions should aim at modulating the immune system rather than simply damping it. In this article, we describe the physiology and pathology of the immune system during obesity and diabetes with a focus on islet inflammation, the IL-1β pathway, and clinical translation.

Introduction

Traditionally, the metabolism and the immune system were perceived as two distinct entities with different functions (nutrient disposal and host defense, respectively). This led to separate specialized research tracks with little interaction between the two fields. In the clinic, interplay between the two systems is often observed. Indeed, steroid hormones are potent immune suppressors and strong inducers of hyperglycemia. Fever is associated with profound changes in metabolism. Some chronic infections may cause a wasting syndrome. More recently, markers of the acute-phase response, including sialic acid, alpha-1 acid glycoprotein, serum amyloid A, C-reactive protein (CRP) and cortisol, and interleukin (IL)-6 were associated with type 2 diabetes and cardiovascular disease (Pickup and Crook, 1998; Pickup et al., 1997; Pradhan et al., 2001; Spranger et al., 2003). In parallel to these well-established associations, an increasing number of scientists working on the multiple disorders characterizing the metabolic syndrome observed that several of its features may be regulated by a pathological activation of the immune system. This holds true for insulin resistance (Hotamisligil et al., 1993), insulin secretion defects (Maedler et al., 2002b), and complications of type 2 diabetes such as cardiovascular (Berk et al., 1990; Ridker et al., 1997) or kidney diseases (Navarro-González and Mora-Fernández, 2008). Therefore, type 2 diabetes can be considered as an inflammatory disease (Donath and Shoelson, 2011).

Beyond these pathological aspects, the involvement of the immune system in the regulation of metabolism may have a primarily physiological role. By definition, the immune system is a system of biological structures and processes within an organism that protects against disease. Such an involvement may also play a role in metabolism. Indeed, several observations point to a beneficial role of the immune system in the adaption to changes in nutrient availability (Ellingsgaard et al., 2011; Maedler et al., 2006). Therefore, we propose that the immune response to an increased amount of nutrients is an adaptive reaction to cope with these changes. Depending on the duration and the degree of metabolic stress, this activation of the immune system may become deleterious. In this article, we will discuss the role of the immune system as a regulator of metabolism, for the good and for the bad, with a focus on islet inflammation, the IL-1β pathway, and clinical translation.

The Immune System in the Physiological Adaptation of Insulin Production and Secretion

Inflammation is not a disease in itself, but rather a manifestation of a disease. Initially, it has beneficial effects such as preventing the spread of infection or promoting regeneration. However, if prolonged or excessive, it may exacerbate disease by tissue destruction. It is likely that, in the case of islet inflammation in type 2 diabetes, similar phenomena occur. Indeed, the endocrine pancreas may adapt to conditions of increased insulin demand (as encountered in obesity and pregnancy) by increasing its functional mass. This may be triggered by limited hyperglycemic events that provoke β cell production of low concentrations of IL-1β followed by Fas upregulation (Maedler et al., 2002a; Maedler et al., 2006). At these concentrations of IL-1β and in the presence of FLICE-like inhibitory protein (FLIP), Fas engagement leads to β cell proliferation and enhanced function via NF-κB and pancreatic and duodenal homeobox 1 (PDX1) (Schumann et al., 2007).

Another example of a physiological role of the immune system is IL-6. The role of IL-6 in the context of glucose metabolism is unclear, and there is an ongoing debate regarding whether IL-6 is deleterious or beneficial (Carey et al., 2006; Jansson and Wallenius, 2007; Lazar, 2005; Mooney, 2007; Pedersen and Febbraio, 2007; Sabio et al., 2008; Weigert et al., 2007; Wunderlich et al., 2010). In support of a deleterious role of IL-6, systemic IL-6 levels are elevated in obese individuals and in patients with type 2 diabetes, and these elevated IL-6 levels predict disease development (Pradhan et al., 2001; Spranger et al., 2003). However, the seminal discovery that skeletal muscle produces and releases IL-6 in response to muscle contraction has challenged the hypothesis that IL-6 is deleterious (Febbraio and Pedersen, 2002). Yet, despite efforts to pinpoint the physiological role of exercise-induced IL-6, this remains to be elucidated fully (Pedersen and Fischer, 2007). IL-6 is necessary for α cell mass expansion after high-fat diet (HFD) feeding (Ellingsgaard et al., 2008). Furthermore, HFD feeding of IL-6 knockout mice results in increased fed glycemia due to impaired insulin secretion, with unchanged insulin sensitivity and similar body weights. Thus, IL-6 is necessary for the expansion of the pancreatic α cell mass in response to HFD feeding, and this expansion may be a compensatory mechanism required for the maintenance of

functional β cells. In a follow-up study (Ellingsgaard et al., 2011), it was shown that elevated circulating IL-6 levels increase plasma levels of the incretin hormone glucagon-like peptide-1 (GLP-1), improving insulin secretion and glucose tolerance. Furthermore, IL-6 induced GLP-1 production and secretion from intestinal L cells and the pancreatic α cells. Hence, IL-6 mediates crosstalk between insulin-sensitive tissues, L cells, and pancreatic islets to adapt to changes in insulin demand by increasing GLP-1 secretion and reprogramming the α cells to process proglucagon to GLP-1.

Overall these studies demonstrate that components of the innate immune system may have very precise roles in the adaptation of the metabolism. It is expected that many more factors are implicated in this physiological role of the immune system.

What Triggers the Innate Immune System during Obesity and in Patients with Type 2 Diabetes?

In All Organs

In obese and insulin-resistant individuals, intake of large amounts of carbohydrates leads to transiently elevated glucose levels defined as impaired glucose tolerance. With time, this prediabetes state may progress to chronic hyperglycemia (i.e., diabetes). Additionally, elevated concentrations of other circulating nutrients, such as free fatty acids (FFAs), are observed in obesity and type 2 diabetes (Boden, 1997). In parallel to increased nutrient concentrations, inflammation is observed in all tissues involved in energy homeostasis, including fat, muscle, liver, and islets, as well as in the nutrient-transporting blood vessels (Berk et al., 1990; Hotamisligil et al., 1993; Maedler et al., 2002b; Navarro-González and Mora-Fernández, 2008; Ridker et al., 1997; Wellen and Hotamisligil, 2005). This association between metabolic stress and inflammation suggests a causal link, which is now supported by experimental data. In vitro FFAs are proinflammatory in many cell types, particularly the saturated long-chain FFAs palmitate (C16:0) and stearate (C18:0) but also the monounsaturated oleate (C18:1), which altogether constitute 80% of the circulating FFAs in humans, while short-chain FFAs (<C14) appear not active with respect to inflammation (Lee et al., 2004; Nguyen et al., 2007; Senn, 2006; Shi et al., 2006; Song et al., 2006). Two main types of mechanisms explaining FFA-triggered inflammation have been proposed, toll-like receptor (TLR)-dependent and TLR-independent types. TLRs are pattern recognition receptors of the innate immune system that can be stimulated by numerous bacterial wall products such as lipopolysaccaride (LPS)-containing long-chain fatty acid moieties. Therefore, it has been postulated that FFAs directly bind to TLRs and thereby induce a proinflammatory response (Lee et al., 2001, 2004). However, recent evidence ruled this out (Schaeffler et al., 2009), and several indirect ways in which FFAs engage TLRs were described. It was reported that FFAs induce the formation of lipid rafts in cell membranes, favoring dimerization of TLRs required for signaling (Holzer et al., 2011; Wong et al., 2009). Others postulated the involvement of an endogenous ligand linking FFA to TLR. An example is the fatty acid transporter CD36, which binds to TLR2 (Seimon et al., 2010). Recently, the liver-derived glycoprotein fetuin-A was identified as the endogenous ligand linking FFA and TLR4, causing inflammation and insulin resistance (Pal et al., 2012). Further, lipid-mediated toxicity may promote damage signals such as high-mobility group protein 1. These are then recognized by TLRs that activate proinflammatory pathways (Park et al., 2004). TLR-independent activation of inflammatory pathways by FFAs involves the production of reactive oxygen species (ROS), which in turn induce stress kinases. ROS may also lead to the formation of NLRP3 inflammasomes, which activates the IL-1 system (Wen et al., 2011). In line with such a mechanism, it was observed in human and mouse islets that the induction of a broad proinflammatory response by FFAs predominantly depends on IL-1 receptor activation. Blocking IL-1 receptor signaling in human islets with the natural receptor antagonist IL-1Ra or the neutralizing anti-IL-1β antibody completely inhibited the induction of cytokines and chemokines by FFAs (Böni-Schnetzler et al., 2009). That both TLR-dependent and -independent mechanisms may operate in concert is indicated by the finding that TLR2- or TLR4-deficient mouse islets are only partially protected from FFA-induced proinflammatory cytokine induction, while the lack of Myd88, which is a universal intracellular docking protein required for both TLR and IL-1 receptor signaling, was fully protective (Böni-Schnetzler et al., 2009).

In vivo short-term infusion of FFAs in rodents or a single fatty meal in humans results in the induction of proinflammatory cytokines and chemokines. In rats, a 2 day infusion with a triglyceride emulsion together with heparin, which results in the breakdown (of triglyceride) into FFAs and a 2-fold increase in plasma FFAs, induces the expression of proinflammatory factors in islets and increases plasma cytokine levels (Tang et al., 2013). Further, infusion of palmitate for only 14 hr in mice induced chemokines in islets and recruited macrophages in a TLR4- and Myd88d-dependent manner (Eguchi et al., 2012). In humans, the consumption of a single high-fat meal increased circulating IL-18 levels (Esposito et al., 2003).

Besides FFAs, elevated glucose levels may also elicit a systemic inflammatory response (Deopurkar et al., 2010). Two mechanisms have been proposed to explain this phenomenon. First, chronic hyperglycemia results in nonenzymatic glycation of proteins and lipids, leading to advanced glycation end products (AGEs), which in turn stimulate the pattern recognition receptor RAGE. RAGE engagement activates the proinflammatory transcription factor NF-κB and stress kinases ERK1 and ERK2 and induces further ROS production (Bierhaus and Nawroth, 2009). RAGE is expressed on various cell types such as macrophages, smooth muscle cells, T cells, podocytes, cardiomyocytes, and neuronal cells (Yan et al., 2009). The second mechanism involves ROS that are formed when excessive glucose is metabolized to ATP via oxidative phosphorylation (Zhou et al., 2010). ROS may then activate the NLRP3 inflammasome in concert with FFAs, leading to the release of active IL-1β and production of IL-1-dependent cytokines and chemokines (Böni-Schnetzler et al., 2009).

In Islets

The first evidence for an inflammatory process in the pancreatic islet arose from the observation that hyperglycemia induces β cell apoptosis (Donath et al., 1999). Unraveling the underlying mechanism (Figure 1), it turns out that high-glucose concentrations induce the Fas receptor, which is upregulated via glucose-induced IL-1β production (Maedler et al., 2001, 2002a, 2002b). Similarly, recent evidence shows that fatty acids also

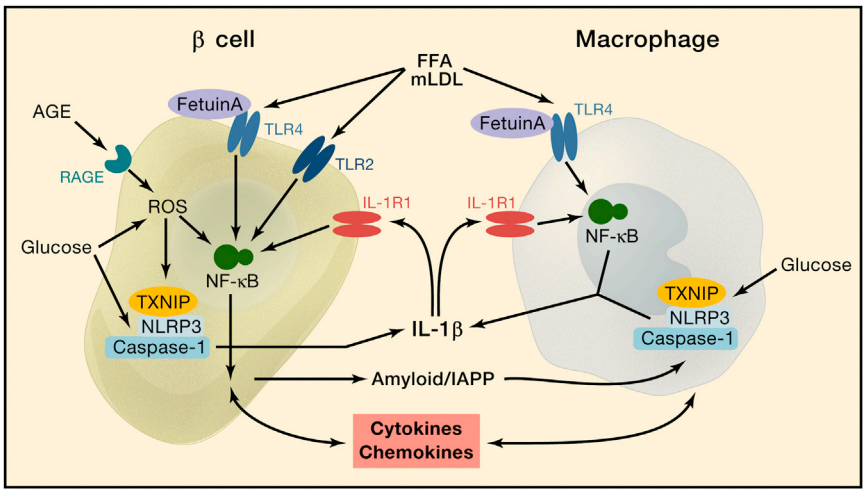

Figure 1. Innate Immune Response to Metabolic Stress in Pancreatic Islets

Increased circulating free fatty acids (FFA), modified LDL (mLDL) particles, and advanced glycation end products (AGE) bind to their cognate receptors (i.e., Toll-like receptor 2 [TLR2], TLR4, and RAGE, respectively), leading to NF-κB activation and the production of various proinflammatory chemokines and cytokines, including the proform of IL-1β. Furthermore, high concentrations of glucose promote the activation of the NLRP3 inflammasome through the recruitment of thioredoxin-interacting protein (TXNIP) in both β cells and macrophages. FFA and AGE, as well as islet-derived islet amyloid polypeptide (IAPP), may also directly trigger the NLRP3 inflammasome complex. Subsequently, pro-IL-1β is processed by the NLRP3-associated caspase-1 and secreted in the microenvironment. In turn, IL-1β sustains autocrine and paracrine activation of both β cells and macrophages, exacerbating the chronic inflammatory responses in the islets.

promote an inflammatory response (Böni-Schnetzler et al., 2009; Ehses et al., 2007; and see above). In support of insulitis in type 2 diabetes, elevated numbers of immune cells have been detected in islets of patients with type 2 diabetes and in animal models in conjunction with increased levels of cytokines and chemokines (Böni-Schnetzler et al., 2008; Ehses et al., 2007; Richardson et al., 2009) (Figure 2B). Of note, every animal model of type 2 diabetes investigated to date displays islet immune cell infiltration (Ehses et al., 2007, 2009a). Furthermore, a strong argument for the occurrence of an inflammatory process in islets is the well-described fibrosis observed in tissue sections of patients with type 2 diabetes, characterized by amyloid deposits. Indeed, fibrosis is a hallmark of the end stage of a chronic inflammatory process. Of interest is the predominant role of IL-1β, which is upregulated in islets of patients with type 2 diabetes (Böni-Schnetzler et al., 2008; Maedler et al., 2002b). This master cytokine regulates numerous other cytokines and chemokines (Dinarello, 2009; Ehses et al., 2009b). Thereby, it contributes to the recruitment of immune cells implementing a broad inflammatory response. It is notable that IL-1β will also induce itself in β cells, engendering a vicious cycle (Böni-Schnetzler et al., 2008). Thus, insulitis may be considered as a fundamental part of the pathogenesis of type 2 diabetes.

Islet β cells have mitochondrial activity 2- to 3-fold higher than any other cell, due to the blood glucose sensing and coupling to insulin secretion via glucose oxidation in mitochondria. Therefore, they are prone to increased ROS production. This may explain the susceptibility of β cells to glucose-induced IL-1β (Maedler et al., 2002b). Indeed, ROS leads to the dissociation of a complex consisting of thioredoxin and thioredoxin-interacting protein (TXNIP) and to the binding of the liberated TXNIP to NLRP3, which initiates the formation of the inflammasome (Zhou et al., 2010) and thus secretion of IL-1β. A combination of elevated glucose together with FFAs is even more effective in inducing a proinflammatory phenotype in human islets (Böni-Schnetzler et al., 2009) and human monocytes (Dasu and Jialal, 2011).

The flux of proteins through the endoplasmic reticulum of β cells is high under normal conditions and increases in the face of insulin resistance. Therefore, endoplasmic reticulum stress may play a role in islet β cell dysfunction in type 2 diabetes (Harding and Ron, 2002). Interestingly, TXNIP is induced by endoplasmic reticulum stress, leading to NLRP3-dependent IL-1β production by β cells (Oslowski et al., 2012).

In support of a specific role for IL-1β in islet inflammation, a recent, unbiased analysis of the global gene expression in human pancreatic islets revealed that a group of coexpressed genes (module), enriched for IL-1-related genes, was associated with type 2 diabetes and reduced insulin secretion (Mahdi et al., 2012). Interestingly, one of the module genes that was highly overexpressed is SFRP4, which encodes secreted frizzled-related protein 4 and may mediate IL-1β effects on islet.

Another specificity of the human pancreatic islets is the deposition of islet amyloid polypeptide (IAPP), which is a typical feature of more than 90% of islets from patients with type 2 diabetes. IAPP is a 37 amino acid long peptide, which (like insulin) is processed by PC1/3 and PC2 from a proform to the mature form and then cosecreted with insulin. Human IAPP rapidly forms aggregates and fibrils, resulting in amyloid depositions. In contrast, rodent IAPP does not aggregate, and only overexpression of the human IAPP in mice and rats results in β cell dysfunction (for review see Westermark et al., 2011). NLRP3 inflammasome formation is reported to be induced by a growing list of compounds, such as urea crystals or asbestos (Hornung et al., 2008; Martinon et al., 2006), and human IAPP was added to the list recently (Masters et al., 2010). Oligomeric human IAPP together with a second trigger induces inflammasome formation and consecutive IL-1β secretion in bone marrow-derived macrophages. This second trigger was either LPS or minimally oxidized low-density lipoproteins. Interestingly, fibrils were less effective than oligomers in these macrophages. Further, expression of elevated IL-1β was observed in islets of mice producing human IAPP, suggesting that IAPP may indeed trigger IL-1β production (Masters et al., 2010). This is supported by observations with a transplantation model in which hIAPP-expressing islets were transplanted to NOD/Scid mice treated with or without the IL-1 receptor antagonist IL-1Ra. IL-1Ra protected transplanted hIAPP-expressing islets from the deterioration of glucose homeostasis in mice transplanted with hIAPP-expressing islets, suggesting that human IAPP impairs β cells via the IL-1 pathway (Westwell-Roper et al., 2011).

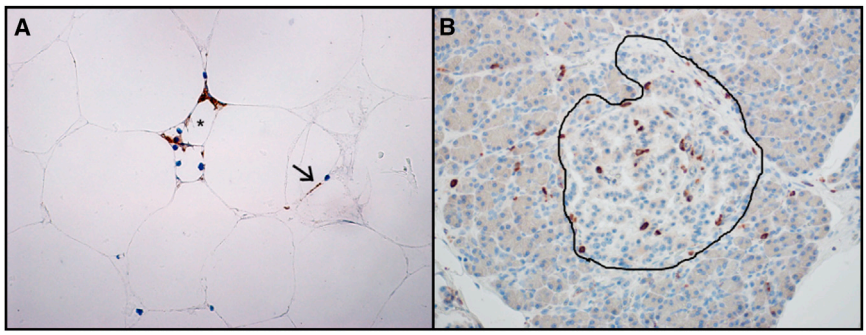

Figure 2. Representative Staining of CD68-Positive Macrophages in Adipose Tissue or Pancreas of Obese Patients with Type 2 Diabetes

(A) Macrophages can be found isolated (arrow) between adipocytes or typically organized in a crown-like structure (*) surrounding a dead-like adipocyte.

(B) Macrophages are isolated and dispersed throughout and around the pancreatic islet (black line).

In Fat Tissues

For two decades now, experimental and clinical data have clearly established that adipose tissue itself is a site of inflammation during obesity. Since the seminal discovery of increased production of tumor necrosis factor alpha (TNF-α) in adipose tissue of obese mice (Hotamisligil et al., 1993), specific upregulation of genes encoding inflammatory factors have become key features of enlarged adipose tissue. More recently, adipose tissue was associated with a marked accumulation of immune cells during obesity (Weisberg et al., 2003; Wu et al., 2007; Xu et al., 2003) (Figure 2A). However, the events that initiate local inflammation are unclear and could involve different, but synergetic, mechanisms (Figure 3). Adipocytes themselves may produce cytokines and chemokines in response to changes in their cell size (Skurk et al., 2007). Eventually, hypertrophy may lead to adipocyte death and release of cellular contents into the extracellular space, triggering an inflammatory response. In particular, macrophages are observed surrounding moribund or dead-like adipocytes in crown-like structures (Cinti et al., 2005; Weisberg et al., 2003; Xu et al., 2003). Progressive lipid accumulation also contributes to the alternative anti-inflammatory M2-to-proinflammatory M1 phenotypic switch in macrophages that occurs in adipose tissue of obese mice (Prieur et al., 2011; Weisberg et al., 2003; Xu et al., 2003). Indeed, adipocyte-derived FFAs or ceramides induce inflammatory responses in macrophages mainly through TLR- or NLRP3-dependent pathways (Nguyen et al., 2007; Vandanmagsar et al., 2011). It has also been proposed that local hypoxia, as a result of vasculature insufficiency in expanding adipose tissue, stimulates inflammatory gene expression in both adipocytes and immune cells (reviewed in Ye, 2009). However, this hypothesis could not yet be confirmed fully in human obesity (Goossens et al., 2011). Alternatively, cellular stress responses, such as the reticulum endoplasmic stress and related autophagy, may be at the origin of local inflammatory signaling pathways in adipose tissue during obesity (reviewed in Hotamisligil, 2010 and in this issue of *Cell Metabolism* by Martinez et al., 2013). Finally, other factors, such as the incretin hormone glucose-dependent insulinotropic peptide, may play a role (Nie et al., 2012; Timper et al., 2013).

In Blood Vessels

Atherosclerosis has long been linked to obesity and dyslipidemia based on a strong clinical relationship between low-density lipoprotein (LDL) levels and atheromatous plaque formation. Classically, proliferation of smooth muscle cells, accumulation of lipids, and connective tissue characterized the pathogenesis of atherosclerosis. However, the involvement of inflammation in atherosclerosis has been recognized for decades (for review, see Galkina and Ley, 2009; Hansson and Jonasson, 2009; Libby, 2012). Although multiple mechanisms initiate and sustain the underlying inflammatory process, we will focus on IL-1β in this part (Figure 4). Galea et al. (1996) found that IL-1β is present in coronary arteries of patients with ischemic heart disease and that the amount correlates with the severity of the atherosclerosis. In addition, human plaques overexpress caspase-1 (also functionally termed IL-1β-converting enzyme; Geng and Libby, 1995). Studies in mice confirmed the role of IL-1β (Elhage et al., 1998) and revealed mechanistic insights, (e.g., knocking out IL-1β in ApoE$^{-/-}$ mice attenuated atherosclerosis by reducing the levels of vascular cell adhesion molecule-1 and monocyte chemotactic protein-1; Kirii et al., 2003). In 2010, cholesterol crystals were identified as a proinflammatory trigger during atherogenesis (Duewell et al., 2010). Cholesterol crystals are a hallmark of atherosclerotic lesions; however, they were thought to be inert and arise only late in the disease. Since the crystals dissolve in organic solvents used in histology, their presence could only be verified by the remaining clefts, of which only large clefts in advanced lesions were identifiable. In their study, Duewell et al. (2010) used a new microscope technique that allowed them to visualize the crystals themselves. They observed that cholesterol crystals emerge at a very early time point of atherogenesis at the same time as immune cells. In vitro, crystallized cholesterol induces the release of IL-1β in macrophages, which depends on the NLRP3 inflammasome-containing ASC and caspase-1. They show that the macrophages internalize the crystals via phagocytosis, leading to the rupture of lysosomes and leakage of the proteolytic content into the cytosol, which is sensed by the NLRP3 inflammasome by a currently unknown mechanism. Freigang et al. (2011) demonstrate that not only is IL-1β secreted by mouse macrophages in response to cholesterol crystals, but IL-1α is also secreted in a caspase-1/NLRP3-independent manner. The induction of both cytokines and their ability to promote atherosclerosis depend upon the NF-E2-related factor 2 (Nrf2). Nrf2 plays a role as a defense mechanism against oxidative stress by increasing antioxidant enzymes; therefore, Nrf2 links oxidative stress to vascular inflammation. In human macrophages, cholesterol crystals have comparable effects (Duewell et al., 2010; Rajamäki et al., 2010). Taken together, cholesterol crystals emerge as an endogenous danger signal in mice and humans, triggering inflammation via the inflammasome-IL-1 axis, and

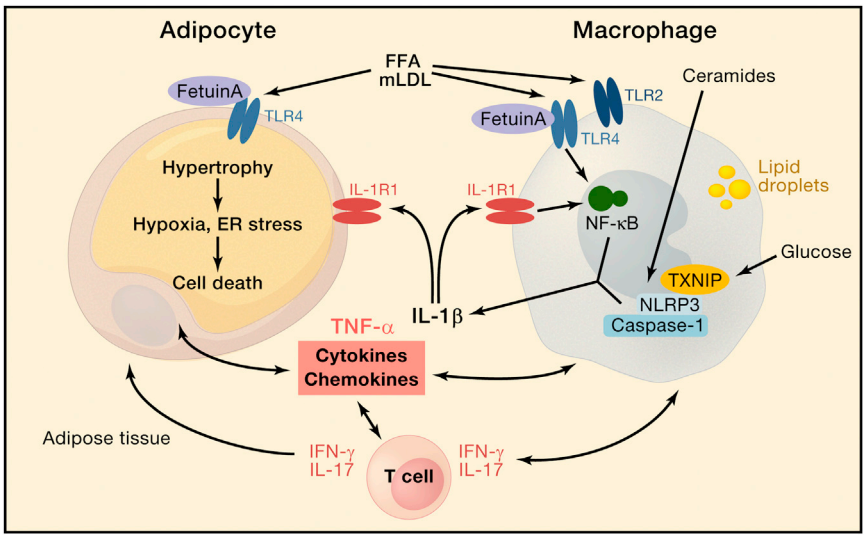

Figure 3. Activation of the Immune System in Adipose Tissue during Obesity

Adipocytes store excessive nutrient load and progressively become hypertrophic. Cell hypertrophy leads to a proinflammatory response mainly through hypoxia and endoplasmic reticulum (ER) stress-related mechanisms. Eventually, this may lead to adipocyte death. Furthermore, stressed adipocytes produce a wide range of cytokines and chemokines, including TNF-α, that in turn promote immune cell accumulation and activation in adipose tissue. Therein, numerous macrophages create a local proinflammatory loop with adipocytes. Other immune cells, such as T cells, might also contribute to inflammation. In parallel, circulating FFAs and mLDL particles may directly bind to TLR2 and TLR4, inducing NF-κB activation and production of various proinflammatory factors including pro-IL-1β. In the meantime, hyperglycemia promotes the activation of the NLRP3 inflammasome through the binding of TXNIP in macrophages. Lipid species such as ceramides may directly activate the inflammasome. The NLRP3-caspase-1 complex promotes IL-1β secretion through cleavage of the proform. IL-1β strongly contributes to adipose tissue inflammation through autoamplification and paracrine activation during obesity.

therefore linking the metabolism of cholesterol to the chronic vascular inflammation that promotes atherosclerosis.

From Innate to Specific Immunity

The current classification of diabetes distinguishes between the autoimmune type 1 diabetes and the adiposity-associated type 2 diabetes. However, in the clinic an overlap exists in many cases of diabetes, and a clear classification is not feasible. Indeed, no single clinical feature or diagnostic parameter completely discriminates the two diseases. This includes age, body mass index, decreased insulin secretion, and insulin resistance. Thus, nowadays type 2 diabetes is diagnosed at a younger age, and increased body mass index has been associated with the observed raise in the incidence of type 1 diabetes. Further, a progressive decrease in functional β cell mass is evident in type 2 diabetes, and although it is not typical to find insulin resistance in patients with type 1 diabetes, its prevalence may be underestimated (Wentworth et al., 2009). Also, the etiology of both types of diabetes is blurring: at least 10% of patients with type 2 exhibit β cell-specific antibodies, and some even exhibit T cells reactive to β cell antigens (Brooks-Worrell et al., 2011), arguing for an involvement of autoimmunity in islets not only in type 1, but also in type 2, diabetes.

Genetic support for the overlap is the recent description of a monogenic form of diabetes with the typical features of type 1 diabetes (autoantibodies to β-cells, lean and young at onset of hyperglycemia, rapid disappearance of C-peptide production, and insulin dependence) together with insulin resistance (Biason-Lauber et al., 2013). This disease is the consequence of an autosomal-dominant mutation in the *SIRT1* gene. The disease pathology may arise as a combined consequence of β cell impairment and death, along with subsequent pathological activation of the immune system. Indeed, in the presence of insulin resistance, stress may accelerate β cell death, which may result in the release of autoantigens together with endogenous danger signals (alarmins) capable of promoting pathologic self-antigen presentation (Zhang et al., 2009). These observations identify a novel role for SIRT1 as a regulator of immune and metabolic functions in humans, thereby linking metabolism to autoimmunity. It is noteworthy that other sirtuins may play a similar role. Indeed, a cellular pathway linking SIRT2 to cytoskeleton remodeling and activation of NLRP3 has been identified recently (Misawa et al., 2013).

At a cellular level, complementary to an ongoing activation of the innate immune compartment, the concept that adaptive immune cells also contribute to obesity-induced inflammation is now established. T cells accumulate in adipose tissue concomitant with early insulin resistance (Rocha et al., 2008; Wu et al., 2007). Mouse models of obesity are associated with increased numbers of cytotoxic $CD8^+$ T effector cells and unchanged or reduced overall $CD4^+$ helper cells in adipose tissue (Nishimura et al., 2009). As conductors of the adaptive immune responses, different $CD4^+$ T helper (Th) lineages exist. Among proinflammatory subsets, classical Th1 and Th17, characterized by secretion of interferon (IFN)-γ and IL-17, respectively, are enriched in the circulation and adipose tissue of obese mice and morbidly obese subjects (Bertola et al., 2012; Duffaut et al., 2009; Jagannathan-Bogdan et al., 2011; Rocha et al., 2008; Zúñiga et al., 2010). Inflammatory and metabolic improvements were achieved in CD8-, IFN-γ-, and (to a lesser extent) IL-17-deleted mice fed a high-fat diet (Rocha et al., 2008; Zúñiga et al., 2010). On the contrary, the numbers of both anti-inflammatory Th2 and regulatory T cells ($Foxp3^+$Tregs) were decreased in the adipose tissue of obese mouse models (Feuerer et al., 2009). More interestingly, humoral immunity with B cell contribution to adipose tissue inflammation was recently brought to light. B cell knockout or anti-CD20 therapy significantly improved the metabolic phenotype and adipose tissue inflammation in mice fed a high-fat diet compared to chow-fed mice (Winer et al., 2011).

Clinical Translation

Based on the information above, it is likely that the immune system plays a significant role in the regulation of metabolism. The

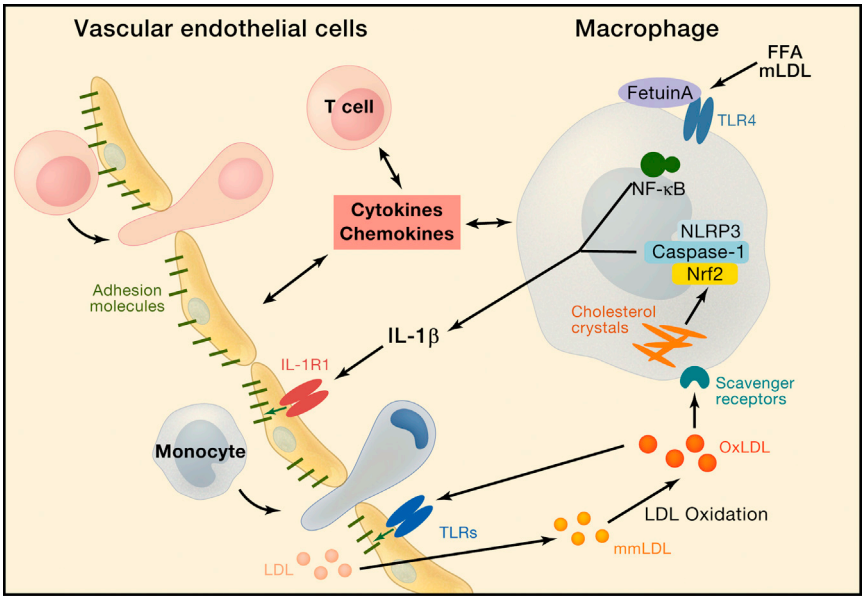

Figure 4. Activation of Innate Immune Responses in the Atheroma

Circulating LDL undergo oxidation in the subendothelial space, from minimally modified LDL (mmLDL) to extensively oxidized LDL (oxLDL). Uptake of oxLDL through scavenger receptors leads to the intracellular storage of cholesterol crystals that can activate the NLRP3 inflammasome through the transcription factor Nrf2, leading to IL-1β secretion. FFAs and mLDL particles can also bind directly to TLRs, leading to the expression of numerous proinflammatory genes such as cytokines and chemokines. These factors, including IL-1β, activate endothelial cells of the vasculature, triggering the production of chemokines and adhesion molecules and, subsequently, other immune cell migration.

next step will be to understand how important these pathophysiological mechanisms are in the development and treatment of type 2 diabetes compared to other pathways. An increasing amount of clinical data may provide answers (Table 1).

TNF-α

Since the initial observation of a potential role for TNF-α in the pathogenesis of insulin resistance and type 2 diabetes (Hotamisligil et al., 1993), numerous clinical trials have attempted to support these preclinical findings. First clinical trials using TNF blockade failed to demonstrate beneficial effects on glucose metabolism (Bernstein et al., 2006; Dominguez et al., 2005; Lo et al., 2007; Ofei et al., 1996; Paquot et al., 2000; Rosenvinge et al., 2007). However, these studies comprised a very limited number of individuals and were conducted only for a short-term period. Because of interindividual variations due to genetic background, possible changes in eating and exercise habits, and the chronicity of the inflammatory changes, these studies were clearly under powered and not designed to allow conclusions about the potential of TNF-α antagonism. Indeed, other studies conducted with obese subjects or patients being treated for additional conditions such as rheumatoid arthritis suggest that TNF-α blockade may alter insulin sensitivity or glycemic parameters (Kiortsis et al., 2005; Stanley et al., 2011; Yazdani-Biuki et al., 2004, 2006). Therefore, well-designed studies are warranted.

Interleukin-1β

The inflammasome appears as the sentinel, sensing metabolic stress and alarming the immune defense in pancreatic islets, insulin-sensitive tissues, and blood vessels. If chronically activated, the resulting production of IL-1β will impair insulin secretion and action. Based on the above observations, numerous clinical studies have been conducted (Cavelti-Weder et al., 2012; Larsen et al., 2007, 2009; Ridker et al., 2012; Rissanen et al., 2012; Sloan-Lancaster et al., 2013; van Asseldonk et al., 2011). All of these studies have shown beneficial effects on blood glucose levels, β cell secretory function, and/or insulin sensitivity. The observed effects depend on starting glycated hemoglobin, concomitant treatment, and pharmacokinetic characteristics, among others. Thus, improvement of glycated hemoglobin varied from 0.2%, which is considered clinically irrelevant, to 0.85%, which is a rather strong effect. Clearly, all of these promising studies are still preliminary, and before the results from large, ongoing studies (see below) are available, no firm conclusion on the magnitude of the effect can be drawn. However, it can be said that the principle of improving diabetes by modulating IL-1β has been demonstrated. Beyond this first conclusion, many additional avenues are opening. Thus, the improvement in insulin secretion following withdrawal of IL-1 antagonism may last at least 39 weeks (Cavelti-Weder et al., 2012; Larsen et al., 2009; Sloan-Lancaster et al., 2013). This may result from the interruption of IL-1β autoinduction (Böni-Schnetzler et al., 2008). Another aspect of IL-1 antagonism is lack of hypoglycemia induction. Indeed, limitations of current treatments, such as insulin and sulfonylurea, include the decrease in blood glucose levels beyond normal values, causing significant untoward effects. In contrast, by improving β cell function with IL-1 antagonism, it is expected that the β cell will release insulin solely following metabolic stimulation. Along this line, the number of hypoglycemic events was not increased by IL-1 antagonists, despite a significant improvement of glycemic control. Furthermore, the development of humanized antibodies against IL-1β provides drugs with a half-life of several weeks, allowing for monthly or even trimestral dosing. Importantly, the drugs appear safe based on the experience gained from the increased use of IL-1 antagonism for several additional therapeutic indications, including in more than 100,000 patients with rheumatoid arthritis. Only rarely have infections been reported, which appeared benign and were easily controlled. Finally, many other complications of diabetes may be caused or promoted by IL-1β-induced inflammation, including nephropathy (Navarro-González and Mora-Fernández, 2008) and cardiovascular complications (Berk et al., 1990; Ridker et al., 1997). Based on this perspective, a large-scale trial of IL-1β antagonism (canakinumab) has been initiated (http://www.clinicaltrials.gov/ct2/show/NCT01327846?

Table 1. Clinical Studies Using Anti-Inflammatory Approaches to Treat Patients with Type 2 Diabetes

Mechanism	Drug	Treatment Duration	Main Findings	Remarks/Limits	Source
IL-1 receptor blockade	anakinra (kineret)	13 weeks	HbA1c ↓; CRP ↓; insulin secretion ↑	dose not adapted to body weight	Larsen et al., 2007
IL-1 receptor blockade	anakinra (kineret)	follow up for 39 weeks	sustained CRP ↓; insulin secretion ↑; insulin requirement ↓	follow-up study of the one above (Larsen et al., 2007)	Larsen et al., 2009
IL-1 receptor blockade	anakinra (kineret)	4 weeks	insulin secretion ↑; insulin sensitivity unchanged	prediabetic patients; underpowered study (13 patients) and short duration	van Asseldonk et al., 2011
IL-1β antagonsim	single dose of anti-IL-1β antibody (gevokizumab)	13 weeks	HbA1c ↓; CRP ↓; insulin secretion ↑	–	Cavelti-Weder et al., 2012
IL-1β antagonsim	anti-IL-1β antibody (canakinumab)	4 weeks	insulin secretion ↑; CRP ↓	short duration	Rissanen et al., 2012
IL-1β antagonsim	anti-IL-1β antibody (canakinumab)	16 weeks	CRP ↓; HbA1c ↓; insulin secretion ↑ (not statistically significant)	underpowered for low basal HbA1c	Ridker et al., 2012
IL-1β antagonsim	anti-IL-1β antibody (LY2189102)	12 weeks and follow up for 24 weeks	HbA1c ↓; CRP ↓; insulin secretion ↑	further improvement of HbA1c at week 24	Sloan-Lancaster et al., 2013
IKK-β-NF-κB inhibition	salsalate	4 weeks	FBG ↓; CRP ↓; insulin sensitivity ↑; adiponectin ↑	short duration	Fleischman et al., 2008
IKK-β-NF-κB inhibition	salsalate	2–4 weeks	FBG ↓; CRP ↓; adiponectin ↑	short duration	Goldfine et al., 2008
IKK-β-NF-κB inhibition	salsalate	1 week	FBG ↓; insulin ↑; CRP ↓	short duration	Koska et al., 2009
IKK-β-NF-κB inhibition	salsalate	12 weeks	HbA1c ↓; FBG ↓; triglyceride ↓; Adiponectin ↑	–	Goldfine et al., 2010
IKK-β-NF-κB inhibition	salsalate	12 weeks	HbA1c ↓; FBG ↓; insulin secretion ↑; triglyceride ↓	drug-naive patient; strong effects on gylcemia	Faqhihimani et al., 2011
IKK-β-NF-κB inhibition	salsalate	12 weeks	FBG ↓; adiponectin ↑	prediabetic patients	Goldfine et al., 2013
TNF-α antagonism	single dose of anti-TNF-α antibody (CDP571)	4 weeks	no effect on insulin sensitivity	underpowered study (ten patients) and short duration	Ofei et al., 1996
TNF-α antagonism	single dose of soluble TNF- Receptor: Fc fusion protein (Ro 45-2081)	48 hours	no effect on insulin sensitivity	underpowered study (seven patients) and short duration	Paquot et al., 2000
TNF-α antagonism	soluble TNF- receptor: Fc fusion protein (etanercept)	4 weeks	CRP ↓; insulin secretion ↑; no effect on insulin sensitivity	underpowered study (ten patients) and short duration	Dominguez et al., 2005
TNF-α antagonism	soluble TNF- receptor: Fc fusion protein (etanercept)	4 weeks	CRP ↓, adiponectine ↑; LDL ↓; no effect on insulin sensitivity	short duration	Bernstein et al., 2006
Decrease of TNF-α and IL-1β by an unknown mechanism of action	diacerein	8.5 weeks	HbA1c ↓; FBG ↓; insulin secretion ↑	drug-naive patient; strong effects on gylcemia	Ramos-Zavala et al., 2011

HbA1c, glycated haemoglobin; IKK-β, IκB kinase-β; NF-κB, nuclear factor-κB; CRP, C-reactive protein; FBG, fasting blood glucose.

term=cantos&rank=1). This trial is now enrolling patients in >35 countries. It will randomly allocate 17,200 patients to placebo or to canakinumab, with all of the participants followed prospectively over an estimated 4 year period for the trial's primary endpoint (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) as well as for new-onset diabetes mellitus and diabetes progression. A specific substudy will assess insulin secretion and sensitivity.

Salsalate

Salsalate is a prodrug of salicylic acid that inhibits NF-κB activity. Several studies have clearly demonstrated its ability to lower blood glucose levels and improve insulin sensitivity (Fleischman et al., 2008; Goldfine et al., 2008, 2010, 2013), and a phase 3 study is ongoing (NCT00799643). Overall the effects are similar to those observed with IL-1 antagonism. This is compatible with the fact that IL-1β activity is largely mediated via NF-κB. However, activation of NF-κB by means other than IL-1β may arouse additional effects. Furthermore, the pharmacological properties of salsalate, which is given orally and has a short half-life requiring several daily doses, differs from anti-IL-1β antibodies, which have a half-life of several weeks. This may explain some differences observed between both treatments. Indeed, while salsalate consistently improved insulin sensitivity, the improvement in insulin secretion was more difficult to detect. This is in contrast to IL-1 antagonism, which reliably leads to improved insulin secretion, while the effect on insulin sensitivity is not always detectable. Furthermore, while both drugs decreased systemic inflammation, as reflected by normalization of white blood cell counts, the effect on C-reactive protein was more consistent with anti-IL-1β treatment. However, between the different studies, there were important variances in the design, the study population, the methods, and the endpoints. Therefore, only direct comparative studies will disclose whether these differences are real.

Anti-Inflammatory Drugs with Unclear Mechanisms

Diacerein is a drug frequently used in the treatment of joint disease due to its anti-inflammatory effects. Diacerein decreases TNF-α and IL-1β, but the mechanism of this effect is unknown. In a recent, promising clinical study, 40 patients with type 2 diabetes were randomized to receive diacerein or a placebo. After two months of treatment, diacerein showed a profound effect on blood glucose levels along with improved insulin secretion (Ramos-Zavala et al., 2011). Other compounds with anti-inflammatory effects have been tested including AC-201, a compound that apparently supresses IL-1β expression. Two phase 2 clinical studies were conducted in patients with type 2 diabetes, and both showed encouraging improvement in glycemia (http://www.twipharma.com). For the time being, these studies should be interpreted with caution, due to the limited information available in the public domain.

Interleukin-6

As mentioned above, IL-6 has pleiotropic effects. The possible involvement of IL-6 in insulin resistance would argue in favor of blocking its activation, while the opposite holds true for its insulin sensitizing effects and for its effect on GLP-1-mediated insulin secretion (Carey et al., 2006; Jansson and Wallenius, 2007; Lazar, 2005; Mooney, 2007; Pedersen and Febbraio, 2007; Sabio et al., 2008; Weigert et al., 2007; Wunderlich et al., 2010). It is possible that, in healthy individuals, IL-6 is a beneficial regulator of glucose disposal, while in the context of obesity, IL-6 will promote the prevailing inflammation and precipitate insulin resistance. However, this remains speculative, and due to the complex effects of IL-6, clinical translation should await the outcome of further studies clarifying the precise role of IL-6 in metabolism and the development of drugs, allowing IL-6 effects to be targeted to a specific tissue (Rose-John, 2012). Nevertheless, existing evidence is sufficient to advise a raise in circulating levels of IL-6 via muscle activity: the beneficial effects of exercise in the prevention and treatment of diabetes is well documented, though it remains to be shown that this is (partly) IL-6 dependent.

Off-Target Anti-Inflammatory Effects of Drugs Used in Patients with Diabetes

Several drugs used with specific indications in patients with type 2 diabetes have anti-inflammatory properties that may contribute to their overall positive effects in outcome studies. The most obvious example being acetylsalicylic acid, often prescribed with the aim to inhibit platelet activation that may have beneficial effects due to its anti-inflammatory feature. However, it is unclear whether the low doses used are sufficient to have a significant anti-inflammatory effect. Better substantiated are the anti-inflammatory effects of statins. An indication was given by the JUPITER study in which healthy persons without hyperlipidemia, but with elevated C-reactive protein levels, were treated with rosuvastatin, which significantly reduced the incidence of major cardiovascular events (Ridker et al., 2008).

Modulation of the renin-angiotensin system may also have anti-inflammatory consequences beyond lowering blood pressure. Several studies with angiotensin receptor blockers found reduced serum levels of TNF-α, IL-6, and/or CRP in patients with hypertension or type 2 diabetes (Fliser et al., 2004; Manabe et al., 2005; Pavlatou et al., 2011). Interestingly, the angiotensin II receptor type 1 is expressed in several immune cell populations, and its signaling regulates T cells as well as monocytes and macrophages (Garcia, 2010). In concordance with this, Fujisaka et al., (2011) show that the angiotensin receptor blocker telmisartan modulates adipose tissue macrophage polarization to an anti-inflammatory M2 state in HFD mice. Supporting these observations, several clinical trials have indicated that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers reduce the incidence of new-onset type 2 diabetes in high-risk populations. This protective effect has been attributed not only to the blood pressure-lowering activity, but also to improved muscle insulin signaling and adipocyte function (Jandeleit-Dahm et al., 2005; van der Zijl et al., 2012). It remains to be shown whether this protective effect is also due to anti-inflammatory effects.

Additional anti-inflammatory drugs currently used for other indications may be tested in the near future. These drugs should be selected on the basis of proven safety profiles in patients. An intriguing example is amlexanox, a drug approved for the treatment of aphthous ulcers and bronchial asthma, which has recently been shown to increase energy expenditure and insulin sensitivity (Reilly et al., 2013).

Alteration of Gut Microbiota in Obesity and Type 2 Diabetes—Strategies for Modulation

Gut microbiota may contribute to obesity and type 2 diabetes (for detailed review, see the article by Cox and Blaser [2013] in this issue of *Cell Metabolism*). Pioneering studies showed that

obesity could be associated with an altered composition of the gut microflora. Ley et al. described that both ob/ob mice and obese subjects were associated with decreased numbers of Bacteroidetes and increased numbers of Firmicutes compared to lean counterparts (Ley et al., 2005, 2006). In rodents, the number of Bifidobacteria was also markedly reduced upon diet-induced obesity (Cani et al., 2007). Such differences in the gut microbiota were shown to promote an altered energy harvest from the diet, essentially through breakdown of otherwise indigestible dietary polysaccharrides. The use of germ-free mouse models or the administration of antibiotics to eliminate gut microbiota in conventionally raised mice both lowered body weight and fat mass during diet-induced obesity (Bäckhed et al., 2004; Cani et al., 2008). Besides, colonization of germ-free mice with microbiota derived from obese mice exhibited greater adiposity than with microbiota derived from lean mice (Turnbaugh et al., 2006). Based on these observations, the question arises as to how modulations of the gut microbiotia could directly influence obesity-induced metabolic outcomes. One hypothesis suggests that high-fat feeding results in LPS-rich microbiota and enhanced LPS translocation into the circulation through increased intestinal permeability (Cani et al., 2007, 2008). The composition of the gut microbiota resulted in LPS-dependent macrophage accumulation in adipose tissue, whereas no correlation was found with systemic glucose metabolism (Caesar et al., 2012). Thus, strategies to manipulate gut microbiota could be an additional approach for the treatment of obesity and type 2 diabetes. Interestingly, beneficial effects of lean fecal microbiota transplantation were recently reported in subjects with the metabolic syndrome, paving the way to the development of new therapeutic designs (Vrieze et al., 2012).

Combined Anti-Inflammatory Treatment

There are several reasons to combine different anti-inflammatory drugs in future treatment strategies of type 2 diabetes. Many inflammatory pathways are involved in the pathogenesis of the disease, and it is unlikely that a single drug will be able to modulate all of them. Some treatments seem to be more effective in improving insulin secretion (anti-IL-1), while others may impact primarily insulin-sensitive tissues (anti-TNF-α, salsalate). Finally, by combining drugs that have a similar target via modulation of different pathways, the amount of untoward effects may be reduced since the off-target effects of the various drugs differ.

Safety Issues

The immune system has multiple tasks including host defense against microbes and clearance of malignant cells. By interfering with this system, the danger of infection or cancer may increase. These and other possible untoward effects can be limited either by using weaker anti-inflammatory drugs or by interfering with a very precise pathway, which plays a central role in a specific inflammatory disease but is less important for host defense or cancer surveillance. Both options exist. Indeed, salsalate acts on multiple pathways, including NF-κB, but is not very potent. This may explain the relative safety of the drug, which can be acquired without a prescription (over-the-counter drug). Other drugs, such as anti-TNF-α antibodies and IL-1 antagonists, efficiently block their respective target molecules and are highly specific. This may explain the somewhat unexpected, excellent safety profile of these drugs. Indeed, both types of drugs have extensively been used for the treatment of several diseases (including patients with rheumatoid arthritis in combination with immunosuppressive drugs) and showed very limited side effects. The main remaining concern is the acceleration of tuberculosis upon TNF-α inhibition, which largely can be avoided by screening the patients for the disease before treatment initiation. IL-1 antagonism minimally increases the incidence of acute infections, which are readily controlled by classic treatments. Due to the specificity of the treatment, it is conceivable that other cytokines compensate to enable an adequate host defense. Another hypothesis is that chronic activation of the innate immune system per se lowers host defense; therefore, restoring homeostasis via specific cytokine antagonists may even improve host defense. However, this is still speculative, and until long-term follow up is available, some safety concerns remain.

Outlook and Conclusions

Obesity and diabetes have reached epidemic dimensions. In the history of medicine, epidemics have only been successfully alleviated via prevention. However, for the affected individuals, additional causative treatment is needed in order to stop the progression of the disease. Inflammation emerges as an important pathogenic pathway not only in the development of diabetes itself but also in the development of its complications. Therefore anti-inflammatory treatment may help affected patients by preventing both the onset and progression of diabetes and its associated comorbidities. However, the immune system is a complex network with beneficial and deleterious elements that show up depending on duration, level, and path of activation and genetic background. It would therefore be naive to expect that single and uniform anti-inflammatory interventions normalize the pathologic activity of the immune system. Rather, we expect multiple interventions with adapted doses and duration. In the meantime, we should be cautious with the interpretation of the first pilot studies and avoid rapid conclusions on the potential of anti-inflammatory treatment of metabolic disease. For the time being, we should be encouraged by the positive outcome of clinical proof-of-concept studies that show that modulation of the immune system can improve glycemia (Fleischman et al., 2008; Larsen et al., 2007).

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