1. ABSTRACT

The incidence of type 2 diabetes (T2D) is rapidly expanding. Some of the more obvious pathologies associated with it include: defective glucose metabolism, obesity, cardiovascular disease and an inability to mount an effective immune response to infection by certain pathogenic organisms, leading to sepsis and death. A common tie linking these seemingly disparate complications is chronic inflammation. Today we know that inflammation is regulated locally and systemically by numerous biochemical signals. One of the most important of these signals is a class of molecules called cytokines. Cytokines can be generally classified as proinflammatory or anti-inflammatory and allow an organism to respond rapidly to an immune challenge by coordinating an appropriate immune response. In T2D, the balance between proinflammatory and anti-inflammatory cytokines is shifted toward proinflammation, potentially causing or exacerbating the health complications found in T2D. Over-nutrition has been shown to trigger the innate immune system but activation of the innate immune system, itself, induces hyperglycemia and insulin resistance. In all likelihood, diabetes and chronic inflammation are inseparable and act as a reciprocal feed-forward loop.

2. INTRODUCTION

T2D affects more than 150 million people worldwide (1) and is projected to increase to 300 million by the year 2020 (2). Unlike type 1 diabetes, which is characterized by an absolute lack of insulin, T2D is characterized by defective insulin function which progresses from subclinical impaired glucose intolerance and insulin resistance to overt diabetes over the course of years (3). Importantly, during this subclinical phase of the disease, health complications such as atherosclerosis and low grade chronic inflammation are already present (4). Inflammation is classically defined by four symptoms: swelling, redness, pain and heat. In 1941, Valy Menkin conducted a series of simple but elegant experiments establishing a firm link between diabetes and inflammation. Menkin found that pancreatectomized dogs injected with an irritant into the pleural cavity showed a nearly 85% increase in blood glucose accompanied by proteolysis, enhanced gluconeogenesis and infiltration with vacuolized polymorphonuclear cells. Non-diabetic dogs showed no change in blood glucose and normal leukocytes after injection of the irritant. Importantly, Menkin was able to block this inflammatory reaction by administration of insulin (5). Menkin’s findings illustrate that inflammation
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enhances the degree of diabetes and diabetes enhances inflammation. Since this initial finding, thousands of studies have improved our understanding of the interaction between diabetes and inflammation. A decade ago, Pickup et al. suggested that T2D was a proinflammatory disease involving activation of the innate immune system (6). In support of this concept, T2D often presents serum elevations of acute-phase reactants including sialic acid, α-1 acid glycoprotein, amyloid A, IL-1beta, TNF-alpaha, IL-6, C-reactive protein, and cortisol (7, 8). Additional studies have shown that altered innate immunity and chronic inflammation appeared strongly associated with insulin resistance in obesity. Uysal et al. reported that the proinflammatory cytokine TNF-alpha was synthesized by adipocytes and was a mediator of insulin resistance in obesity (9). Kim et al. demonstrated that inactivation of IKK-beta prevented fat-induced insulin resistance in skeletal muscle, suggesting it as a potential therapeutic target for T2D (10). Cai et al. demonstrated that NF-kappaB activation and proinflammatory cytokine production (including IL-6, IL-1 and TNF-alpha) were increased in the liver by obesity and high-fat diet, leading to insulin resistance and hyperglycemia (11). A study by Solinas and coworkers showed that inflammation but not obesity per se, triggered insulin resistance. In mice, high-fat diet-induced insulin resistance could be prevented through blocking an inflammatory pathway in macrophages by JNK1 deletion (12). These results connote that obesity-induced inflammation decreases high-fat diet-induced insulin resistance as well as resultant T2D. Recent data have shown that increased levels of inflammatory cytokines, such as IL-6 and high-sensitivity C-reactive protein (hsCRP), were linked to an elevated risk of clinical diabetes (13-15). Work by our group indicated that the enhanced proinflammatory phenotype in T2D not only affected complications like cardiovascular disease (16) but also exacerbated other pathologies such as depression and social withdrawal induced by activation of the innate immune system with lipopolysaccharide (17) or hypoxia (18).

In addition to elevation of proinflammatory cytokines, T2D may be associated with a less effective anti-inflammatory response. The process of insulin resistance has been an area of prolific study. There are several factors that can lead to insulin resistance including increased degradation of the receptors by the proteasome, alteration of downstream signaling partners and phosphorylation at inhibitory serine and threonine residues (19). One of the critical regulators of this process is a class of molecules called suppressor of cytokine signaling (SOCS). Interestingly, several anti-inflammatory cytokines including IGF-1, IL-4 and IL-10 share key signaling components with the insulin receptor and are susceptible to similar resistance mechanisms.

3. PROINFLAMMATORY CYTOKINES

There are a variety of cytokines labeled as proinflammatory. Almost all immune cells as well as epithelial cells and adipocytes produce a subset of these cytokines. Generally, proinflammatory cytokines are important for initiating the innate immune response and for directing the subsequent adaptive immune response. The most studied contributors to the chronic inflammation seen in T2D are leptin, TNF-alpha, IL-1beta, and IL-6.

3.1. Leptin

Leptin was first discovered after a series of parabiosis experiments (20). Coleman infused the plasma of obese, hyper-leptinemic db/db mice into wild-type mice. Surprisingly, the mice became anorexic and died of starvation. Zhang et al. cloned the gene encoding the 16 kDa leptin protein (21) while the gene encoding the principal leptin receptor was identified by Leiter et al. (22). The crystal structure of leptin revealed a four-helix bundle similar to that of IL-6 (23). The action of leptin is primarily mediated through Janus kinase-2 (JAK-2) and signal transducer and activator of transcription-3 (STAT-3) (24). Targeted disruption of STAT-3 in the central nervous system induces a phenotype similar to mice lacking either leptin or the leptin receptor ie. obesity, diabetes and infertility (25). Importantly, leptin has also been shown to act on pathways that include those containing insulin receptor substrate (IRS), phosphotydilinositide 3’-kinase (PI3K), mitogen activated protein kinase (MAPK) (26) and, recently, AMP-activated protein kinase (27) (for a complete review see (28)).

Leptin is a multifunctional cytokine. It is secreted primarily by adipose tissue but many other tissues can produce it, including macrophages. Leptin is best known as a regulator of satiety and energy homeostasis (29). It acts as a permissive signal when energy levels are high, as represented by adequate fat stores. However, when energy stores are low, leptin secretion decreases and the orexigenic system is activated in the hypothalamus, causing feelings of hunger (29). Human studies that attempted to reduce food intake by exogenous administration of leptin have been disappointing (30). A number of theories were raised to explain this lack of appetite suppression. One theory is that leptin receptors are highly expressed in the satiety centers of the hypothalamus, but in order to bind to these receptors, circulating leptin must pass through the blood brain barrier via a saturable process (31). It is possible that the high circulating leptin levels observed in obese individuals do not result in similar increase in brain leptin. Interestingly, Faouzi et al. have shown that specific hypothalamic regions establish a direct contact with the general circulation, and thereby, display differential patterns of leptin uptake and responsiveness (32). Another mechanism potentially explaining the lack of therapeutic benefits of leptin is that individuals may acquire leptin resistance (33) in a manner similar to insulin resistance, including the disruption of downstream leptin receptor signaling by SOCS proteins (34).

Leptin has a number of important functions in immunity. It has been shown to induce the production of TNF-alpha, IL-1beta, IL-1RA, IL-R2 and IL-6 as well as that of reactive oxygen species, and to increase phagocytosis in some antigen presenting cells (35-37). Recently, a role of leptin in the regulation of emotions and depression has been suggested. db/db mice lacking a functional long form of the leptin receptor showed delayed recovery from LPS- or hypoxia-induced social withdrawal.
3. IL-6

IL-6 is a 27 kDa four helix-bundle cytokine with structural similarity to leptin (56). The IL-6 receptor is a heterodimer consisting of a gp130 subunit and IL-6R. IL-6 directly affects many tissues including B cells, T cells, megakaryocytes, macrophages, hepatocytes, osteoclasts, blood vessels, heart muscle, neuronal cells and the placenta (57). IL-6 is produced mainly by cells of the immune system, skeletal muscle and the liver, but other cells types such as glia and endothelial cells have been reported to produce IL-6 (58). The effects of IL-6 differ according to the target tissues. IL-6 is a key regulator of the acute phase response by the liver following infection. It induces the production of C-reactive protein, haptoglobin, serum amyloid A and fibrinogen (59). Like leptin, IL-6 signaling occurs through the MAP kinase, and the JAK/STAT pathways (60). IL-6 is a potent endogenous pyrogen and augments LPS induced sickness behavior (61).

The role of IL-6 in T2D is complex and appears to be tissue dependent. Circulating levels of IL-6 levels are increased in T2D (7). A chronic overexpression of IL-6 appears to reduce the action of insulin like growth factor in mice displaying growth defects. This effect was partially neutralized by the administration of anti-IL-6 receptor antibodies (62). In addition, IL-6 has been shown to promote insulin resistance in hepatocytes through the activation of STAT-3 (63). This mechanism was further elucidated by the finding that insulin resistance in hepatocytes was mediated by SOCS-3 and that mTOR played a critical role in SOCS-3 upregulation (64). Additionally, Cai et al. showed that T2D could be induced in mice by chronic activation of NF-kappaB in the liver or a high fat diet. These chronic inflammatory conditions induced steatosis of the liver and an increase production of proinflammatory cytokines by hepatocytes, including IL-6. Importantly, insulin resistance could be significantly improved by treatment with IL-6 neutralizing antibodies or salicylate (11). These findings suggested a causative role for IL-6 in the development of T2D. However, mice with a targeted deletion of IL-6 developed mature-onset insulin resistance, obesity and leptin resistance (65). It was speculated that the reason for this contrary finding was that the action IL-6 is tissue dependent. Indeed, the local administration of IL-6 into the brains of IL-6 deficient mice partially improved the aforementioned symptoms but it had no effect when administered into the brain of wild type control animals (66). The importance of tissue specificity was further emphasized by the finding that IL-6 enhanced insulin-stimulated glucose disposal and improved glucose metabolism in humans through the activation of AMPK, likely in skeletal muscle (67). IL-6 is clearly an important cytokine in the regulation of immunity and metabolism and it may be an important player in the development and complications of T2D. Further research will be necessary to clarify the absolute impact of IL-6 in T2D.

4. CYTOKINES RESISTANCE

Counter-regulations are critical to maintain homeostasis. One of the most important mechanisms of hormone/cytokine counter-regulation is mediated by the SOCS family of proteins. While investigating the
to explain how dysregulation in certain immune pathways Additionally, there now appears a direct mechanistic path SOCS proteins as key immune and metabolic regulators. adding to the growing body of evidence that implicates the inflammatory cytokine IL-4 to induce IL-1RA by (70), proteins negatively impacted the efficacy of the anti-demonstrated that T2D-dependent upregulation of SOCS protein-mediated insulin resistance (64). Recently, it was shown to act as an anti-inflammatory agent by activating AMPK (76). Use of metformin is interesting because AMPK is a key local and systemic metabolic regulator. In addition, these findings underscore the degree of integration between metabolism and immunity. Finally and very recently, IL-1RA has shown promise in improving glycemia, beta-cell secretory function and reducing markers of systemic inflammation (77). By expanding our understanding of T2D, we have increased the therapeutic options available to the individual with diabetes, and have, in some ways, returned to Ebstein’s original observations with the archetypal anti-inflammatory aspirin (73).

6. CONCLUSIONS

Inflammation can be viewed as a homeostatic model with pro- and anti-inflammatory aspects. Proinflammatory cytokines are necessary in order to mount an initial effective immune response. However, this proinflammatory reaction must be balanced by an appropriate anti-inflammatory rejoinder in order to effectively direct the adaptive immune response and to avoid excessive damage to healthy tissues. Furthermore, the immune response must be in balance with the metabolic supplies of the organism. Immune and metabolic pathways are deeply intertwined (Figure 1) and require synchronicity in order to promote organismal survival (78). T2D is a key example of what happens when balance goes awry. Neither cytokine nor hormonal networks function in isolation so it is likely that many important future contributions to our understanding of T2D will be found by examining the complicated interaction and temporal variations of immune/metabolic balance. While tremendous strides have been made in understanding the nature of T2D and its complications, much more work needs to be done to improve the lives of these individuals living with the all too familiar quartet of swelling, redness, pain and heat.

7. ACKNOWLEDGEMENTS

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