10.1 Inflammation Is an Important Feature of Metabolic Diseases and Diabetes

Diabetes mellitus, referred to simply as diabetes, is a serious metabolic disorder that affects millions of people worldwide [1, 2]. It is caused by defects in insulin production, insulin secretion, and insulin signaling, all of which result in abnormally high blood sugar levels [3]. Diabetes patients usually develop serious secondary complications, especially involving the microvasculature but also cardiovascular disease, retinal damage, nerve damage, and kidney failure [4]. The two principal idiopathic forms of diabetes are known as types 1 and 2. Type 1 diabetes (T1D) is due to an autoimmune attack that leads to self-destruction of the insulin-producing β-cells of the pancreas. Type 2 diabetes (T2D) is caused by defects in insulin action and production, leading to insulin resistance, dyslipidemia, and impaired insulin secretion.

10.1.1 Peripheral and Adipose Inflammation

The exact etiology of T2D is currently unknown, as the pathogenesis of the characteristic insulin resistance and/or impaired insulin secretion is unclear. However, following up on the hypothesis formulated by Pickup et al. in 1997 and 1998, recent studies have shown that innate immunity, stress and acute-phase responses, and more specifically inflammation play leading roles in the development of obesity-related insulin resistance in T2D [5-9]. Indeed, compared to T1D patients, those with T2D generally test positive for serum pro-inflammatory cytokines such as C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α [9]. For exam-
ple, studies directly linking these pro-inflammatory cytokines to T2D have shown that in obese rodents TNF-α levels are elevated in adipose tissues and blood samples and that neutralization of TNF-α can greatly improve insulin sensitivity in these animals [9, 10]. TNF-α causes insulin resistance by indirectly phosphorylating insulin receptor substrate (IRS)-1 and IRS-2, thus inhibiting insulin signaling [11, 12]. It has been proposed that lipid accumulation in adipocytes, inducing a state of cellular stress marked by activation of JNK and NF-κB, leads to an increase in the secretion of TNF-α and other pro-inflammatory cytokines [13]. The pro-inflammatory cytokines IL-6 and CRP are also capable of decreasing insulin sensitivity, either by degrading the peroxisome proliferator-activated receptor γ (PPARγ), a key regulator of normal insulin sensitivity, or by inducing the suppressor of cytokine signaling proteins (SOC), which targets IRS for degradation [11, 12, 14].

The pro-inflammatory response in T2D is activated via the JNK/activator protein 1 (AP1) and IKK/NF-κB signaling pathways in adipose tissue [15]. This can, in turn, lead to cell death or to the establishment of a characteristic inflammatory response that involves the recruitment of macrophages. The subsequent release of pro-inflammatory cytokines by macrophages results in enhanced activation of the JNK1 and IKK/NF-κB pathways [16]. In a positive feed-forward loop, the activation of these pathways induces chemokine release, which again recruits macrophages to adipose tissue. Finally, a pro-inflammatory site is established that causes insulin resistance also in neighboring adipocytes via paracrine effects [9, 16]. The pro-inflammatory role of adipocytes is also a consequence of their secretion of free fatty acids (FFAs) and adipokines such as leptin and adiponectin, both of which promote insulin sensitivity [9, 17].

10.1.2 Islet Inflammation

The pancreatic islets of patients with T2D undergo apoptosis due to a severe process of inflammation and functional exhaustion. Among the factors that mediate islet destruction are leptin, IL-1β, TNF-α and lipoproteins. Thus, leptin is not only involved in insulin secretion; it is also capable of inducing pancreatic β-cell apoptosis by enhancing the release of IL-1β and diminishing that of IL-1 receptor antagonist in human islets [18]. The release into the blood stream of FFAs and lipoproteins, which is usually a direct consequence of obesity in T2D patients, is detrimental to β-cells as it provokes a reduction in insulin content, abnormally elevated insulin release in the absence of stimuli, and a diminished capacity of these cells to secrete insulin in response to glucose [19-21]. Moreover, some fatty acids, such as palmitate, are capable of inducing β-cell apoptosis by [22, 24]. Studies carried out by Solinas et al. and Arkan et al., utilizing IKKβ- or JNK1-knockout mice, showed that either strain of knockout mice was resistant to induced glucose intolerance, hyperinsulinemia, and insulin resistance in adipose and skeletal muscle tissue [25, 26]. Given that these mice developed the same degree of obesity as their wild-type counterparts, it seems that obesity itself cannot cause insulin resistance without a functional inflammatory component. The active role of IL-1β in β-cell impairment and apoptosis led to the