1. Introduction

Low physical activity and hyperalimentation with energy-dense food are the environmental factors currently leading to the world-wide epidemic of obesity. These factors have been shown to be more or less directly associated with an increased risk of T2DM (1). Insulin resistance and impaired beta-cell function are the two intermediate phenotypes finally leading together to manifestation of type 2 diabetes mellitus (T2DM) (2). T2DM is associated with an increased risk of cardiovascular disease, which is the most frequent cause of mortality in the modern world.

Despite more than millions of patients affected worldwide and a substantial socio-economic burden due to the cardiovascular and microvascular complications, the aetiology of T2DM is not yet completely understood. There is now cumulating evidence that cytokines play a major role in this process although the relationship is mostly non-linear and these mediators might be beneficial in one setting, while they appear to be detrimental in another. For example, Interleukin-6 (IL-6) is elevated in obesity and given as a recombinant protein, it affects lipid metabolism and elevates circulating free fatty acids (3, 4). In adipose tissue, IL-6 appears to suppress the expression of the insulin sensitising cytokine adiponectin (5) and in epidemiological studies high levels of IL-6 were found to be associated with an elevated diabetes risk (6, 7). However, IL-6-KO mice are obese and central application of IL-6 is able to reverse this effect (8). Thus one needs to take the specific environment into account to precisely understand the relation between cytokines and a specific phenotype. Especially it is important to keep in mind that cytokines operate as networks rather than as isolated factors.

Given the pleiotropic nature of most cytokines it is not surprising that they play a role not only in the pathogenesis of diabetes but also in diabetes-associated

microvascular complications, which both will be demonstrated for some specific cytokines within this work. Although the manuscript will primarily focus on previously published work of the applicant, some yet unpublished data will also be shown, if appropriate. All data will be demonstrated within the respective scientific context.

2. Cytokines and type 2 diabetes mellitus

2.1 Inflammation and type 2 diabetes mellitus

As early as 1876, the first report on glucose lowering effects of the anti-inflammatory effects of salicic acid has been reported in the *Berliner Medizinische Wochenschrift* (9). Although this effect was not further evaluated until the early sixties, it is now becoming increasingly clear that T2DM is a manifestation of an ongoing acute-phase response, which is primarily characterized by alterations of the so called acute phase proteins such as C-reactive protein (CRP) (10, 11). Cross-sectional and prospective studies demonstrated increased concentrations of inflammatory markers, including CRP, serum amyloid-A and sialic acid in patients with T2DM (6, 7, 10-17). Elevated levels of IL-6, a major stimulator of acute-phase proteins, were demonstrated to be associated with an elevated risk of diabetes mellitus (7). However, it is well known, that cytokines operate as a network in stimulating the production of acute-phase proteins. Thus, the effects of IL-6 on CRP synthesis depend on an interaction with Interleukin-1ß (IL-1ß) (18). The acute-phase response in various artificial inflammatory models requires both IL-6 and IL-1ß as demonstrated in the respective knock-out mice models (19, 20). Recent work of the applicant extended this field with respect to the polycystic ovarian syndrome (PCOS), a disease being associated with