

Zusammenfassung

Typ-2-Diabetes ist mit einer subklinischen systemischen Entzündung verbunden. Erhöhte systemische Spiegel an Glykoproteinen und Akutphaseproteinen sowie erhöhte Leukozytenzahlen in Patienten mit Typ-2-Diabetes wurden bereits in den 1960er-Jahren in Querschnittsstudien nachgewiesen. Später zeigten prospektive Studien, dass erhöhte Spiegel verschiedener Akutphaseproteine und Zytokine prädiktiv für die Entwicklung eines Typ-2-Diabetes sind. Immungenvarianten modulieren im Tiermodell und im Menschen Insulinresistenz und Diabetesinzidenz und die Therapie des Typ-2-Diabetes mit Pharmaka, Ernährung oder körperlicher Bewegung reduziert signifikant die systemische Konzentration verschiedener Immunmediatoren. Immunologische Untersuchungen im Rahmen des KORA-Surveys S4 (1999/2001) belegten, dass die Konzentrationen von zirkulierenden Akutphaseproteinen wie CRP stark mit den Serumspiegeln von IL-6 korrelieren und nicht nur bei manifestem Typ-2-Diabetes, sondern bereits im Stadium der gestörten Glukosetoleranz erhöht sind. Dies deutet darauf hin, dass diese Mediatoren in die Pathogenese des Typ-2-Diabetes involviert sind. TNF α hingegen war weder mit CRP koreguliert, noch mit dem Diabetesstatus assoziiert. Unsere Ergebnisse zeigen daher, dass Typ-2-Diabetes von einer nicht-zufälligen und differenziell regulierten Aktivierung der natürlichen Immunität begleitet

Abstract

Type 2 diabetes is associated with a systemic low-grade inflammation. First data provided by cross-sectional studies from as early as the 1960s demonstrated elevated systemic levels of glycoproteins and acute-phase reactants and increased leukocyte counts in type 2 diabetes patients. Subsequently, prospective studies showed that elevated concentrations of several acute-phase proteins and cytokines are predictive of later type 2 diabetes. Immune gene variants in man and in animal models were found to affect insulin resistance and diabetes incidence. Anti-diabetic treatment by medication, diet or physical activity results in a significant decrease of systemic immune mediator concentrations. Immunological analyses of the KORA Survey S4 (1999/2001) allowed us to show that levels of circulating acute-phase proteins like CRP and of IL-6 are highly correlated and associated not only with overt type 2 diabetes, but already with impaired glucose tolerance (IGT) pointing out a role of these mediators in the pathogenesis of type 2 diabetes. On the contrary, TNF α was neither coregulated with CRP nor associated with diabetes status. Our study therefore shows that type 2 diabetes is accompanied by a non-random and differential upregulation of components of the innate immunity and suggests that this inflammatory condition is involved in the aetiology of the

note

The KORA study group consists of H.-E. Wichmann (speaker), H. Löwel, C. Meisinger, T. Illig, R. Holle, J. John and co-workers who are responsible for the design and conduct of the KORA studies.

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wird, und implizieren, dass dieser Entzündungsstatus mit der Entstehung der Erkrankung in engem Zusammenhang steht. Weitere Arbeiten werden das Spektrum der Untersuchungen auf Chemokine ausdehnen und die Assoziation der Immunmarker mit Adipositas prüfen, um zu klären, ob dieser klassische Diabetes-Risikofaktor relevant für die Entstehung der subklinischen Entzündung ist.

Schlüsselwörter

Diabetes · gestörte Glukosetoleranz · Entzündung · Interleukin-6 · natürliche Immunität

disease. Future work will extend the range of analysed immune mediators to chemokines and will also investigate the association of immune markers with indices of obesity to elucidate the relevance of this traditional risk factor for low-grade inflammation.

Key words

Diabetes · impaired glucose tolerance · inflammation · interleukin-6 · innate immunity

Introduction

The link between type 2 diabetes and inflammation has been the research focus of many groups since 1997/1998 when Pickup and colleagues postulated that chronic subclinical inflammation and activation of the innate immunity are involved in the pathogenesis of this disorder [1, 2]. Data have, however, been accumulated since as early as the 1960s that the systemic concentration of many immune mediators in the circulation appears chronically upregulated in diabetes [3–8]. Reports can be grouped into four main lines of evidence:

(i) First data to give rise to the inflammation hypothesis came from cross-sectional studies which compared patients with prevalent type 2 diabetes or metabolic syndrome and normoglycaemic controls or searched for a correlation between immune mediators and measures of insulin resistance in non-diabetic individuals. These studies described the association of type 2 diabetes and elevated levels of acute-phase proteins like C-reactive protein (CRP), cytokines like interleukin-6 (IL-6) and other markers of leukocyte or endothelial cell activation [9 and references therein, 10]. In order to address the question whether immune activation is cause or consequence of diabetes, cross-sectional studies should also include patients with impaired glucose tolerance (IGT), who have a significantly higher risk to develop type 2 diabetes than age- and sex-matched controls.

(ii) Important contributions to the discussion were made by prospective studies which investigated whether alterations of inflammatory markers in a subset of a cohort predict the development of type 2 diabetes and diabetes-related complications. The remarkable recent finding that in different ethnic groups including Central Europeans from the MONICA Augsburg population elevated white blood cell count and concentrations of circulating immune mediators, CRP and IL-6 in particular, are present many years before disease manifestation strongly emphasises the importance of activated innate immunity [9 and references therein, 11]. Interestingly, only a single marker has been described as yet which appears to be protective: The adipocyte-derived cytokine adiponectin combines insulin-sensitising and anti-inflammatory properties, and high levels of serum adiponectin are associated with significantly reduced risk of diabetes development [12, 13].

(iii) Insights from serological studies are complemented by a wide range of observations that immune gene variants in humans as well as knockouts or transgenic overexpression of im-

mune mediators, their receptors and other immunologically relevant proteins such as inducible NO synthase (iNOS) are associated either with higher diabetes prevalence or with protection from diabetes [9 and references therein]. There are inherent limitations of the genetic approach. Some of the described immune gene alleles might turn out to be false-positives because they are in linkage disequilibrium with a disease-modifying non-immune gene allele. Furthermore, gene disruption and transgenesis in inbred animal models may represent too gross disturbances of the delicate immunological networks to reveal subtle pathogenetic pathways in the etiology of type 2 diabetes in human populations. However, the ever increasing number of clinical studies reporting associations of polymorphisms in promoters and within exons and introns of immune genes [50] and exploring the impact of ethnicity on immune status and diabetes prevalence steadily erode the immunosceptical position.

(iv) Finally, there are numerous studies on the effects of pharmacological interventions or lifestyle and behavioural factors both on measures of insulin resistance or diabetes development and on inflammation. Insulin and oral antidiabetic drugs like glitazones and metformin are known to lower the activation state of systemic immunity [14–19]. Environmental and lifestyle factors as diverse as physical activity, body weight changes, nutrition (fatty acids, advanced glycation end products/AGEs, alcohol), birth weight and psychological stress have all been postulated or shown to be associated with modulation of systemic immune marker concentrations and diabetes risk [10 and references therein]. Data from the Finnish Diabetes Prevention Study demonstrate that nonpharmacological intervention focussing on physical activity and diet can indeed lead to decreased risk of diabetes development paralleled by attenuation of subclinical inflammation ([19], C. Herder, H. Kolb, unpublished data).

In the context of the aforementioned data, the KORA S4 offers a unique opportunity to investigate the interplay of inflammation and type 2 diabetes. Major strengths of the KORA S4 are (i) the population-based approach with a sufficiently large group of participants to compare patients with 2 diabetes and normoglycaemic controls and also to extend the analyses to age- and sex-matched patients with IGT, (ii) the gold standard of diabetes diagnosis by oral glucose tolerance test (OGTT) in order to include hitherto undiagnosed cases, (iii) the analysis of autoantibodies to exclude cases of latent autoimmune diabetes of adults (LADA) and (iv) the meticulous phenotypic characterisation of clinical, biochemical and socioeconomic parameters leading to an im-

mensely valuable database. The aim of this article is to summarise and discuss previously published relevant results from the KORA S4 [22] and to give an overview about ongoing and future projects which will elucidate the contribution of the immune system to diabetogenesis.

Methods

Study population

The study population has been described extensively in a previous report [20] and elsewhere in this issue. Briefly, the KORA (Cooperative Research in the Region of Augsburg) S4 survey (1999/2001) studied a representative sample of the general population of German nationality in the Region of Augsburg. The survey comprised 4,261 subjects aged 25–74 years with a response of 67%. The study was carried out in accordance with the Declaration of Helsinki as revised in 1996 and approved by the Ethics committee of the “Bayerische Landesärztekammer” Munich. Our study focuses on a subset of 1,653 persons in the age range of 55–74 years who participated in a standardised interview followed by biochemical and clinical analyses.

Diabetes diagnosis

All individuals without known diabetes were subjected to an OGTT performed according to a standardised protocol. Diabetes and IGT were diagnosed according to 1999 WHO criteria. Patients with type 1 diabetes or LADA were excluded on the basis of their titre for autoantibodies against glutamic acid decarboxylase (GAD). GAD titres above the 99th percentile in healthy controls (6.5 GAD antibody units) were considered positive.

Laboratory methods and statistical analysis

Plasma CRP concentrations were assessed by a high sensitivity latex enhanced nephelometric assay [21]. Serum levels of IL-6, TNF α and their respective soluble receptors were determined by rigidly evaluated sandwich ELISAs as described previously [22]. All ELISAs were optimised to meet the following criteria: linearity of signal for the standard curve between optical density (OD) 0.05 and 2.0, difference between expected and measured signal in spiking experiments less than 15%, mean intra-assay variation below 10%, mean inter-assay variation below 10%, no signal reduction for IL-6 and TNF α in the presence of their respective receptors. An interference of heterophile antibodies was not observed. Detection of limits were 0.24 pg/ml for IL-6, 1.54 ng/ml for sIL-6R, 0.16 pg/ml for TNF α , 0.02 ng/ml for sTNF-R60 and 0.2 ng/ml for sTNF-R80. Differences in immune mediator concentrations between groups were compared by Kruskal-Wallis test (three groups) and, if significant, followed by the Wilcoxon test for multiple testing. Spearman rank correlation coefficients were used to analyse associations between continuous variables. The level of significance was 0.05.

Results

Study population

The analysis of the association of immune markers with diabetes and IGT is based on a subgroup of randomly selected individuals

with IGT (n = 80) and age and sex matched patients with type 2 diabetes (n = 71 with known history of type 2 diabetes, n = 81 newly diagnosed) and non-diabetic controls (n = 77). Compared with controls, patients with type 2 diabetes had significantly higher body mass indices, elevated levels of triglycerides, higher systolic blood pressure, increased prevalence of hypertension and decreased HDL cholesterol [22]. Patients with IGT differed from controls by significantly increased body mass index, higher levels of fasting plasma glucose and triglycerides, higher systolic blood pressure and increased prevalence of hypertension [22]. There were no significant differences regarding the prevalence of coronary heart disease or cardiovascular disease.

Concentrations of CRP and of IL-6, TNF α and their soluble receptors

Median plasma concentrations of the acute-phase proteins CRP (Fig. 1a), serum amyloid A (SAA) and fibrinogen (data not shown) were significantly higher in individuals with type 2 diabetes and IGT compared to controls, whereas the levels between diabetic patients and subjects with IGT did not differ. Exclusion of all individuals with high CRP concentrations (more than 10 mg/l), which could be attributable to confounding infections, confirmed these observations.

Measurement of the cytokine IL-6 also revealed significantly elevated concentrations of this immune mediator in the IGT group compared to controls and even higher IL-6 levels in the type 2 diabetes group (Fig. 1b). Since IL-6 and soluble IL-6 receptor (sIL-6R) act synergistically, we tested the hypothesis that the increase of IL-6 could be counterregulated by reduced sIL-6R concentrations. As shown in Fig. 1c, sIL-6R levels showed the same trend as IL-6, although only the difference between type 2 diabetes patients and controls reached statistical significance. On the individual level, serum concentrations of IL-6 and sIL-6R were significantly correlated ($r = 0.15$, $p < 0.01$).

Contrary to the data for IL-6, TNF α levels were not significantly elevated in type 2 diabetes patients compared to controls, although they were higher than in the IGT group (Fig. 1d). Concentrations of soluble TNF α receptors sTNF-R60 and sTNF-R80, which have been described to reduce TNF α activity in the circulation, were even increased in type 2 diabetes patients compared to controls (sTNF-R60 and sTNF-R80) and to subjects with IGT (sTNF-R80 only) (Figs. 1e, 1f).

The differences between the association of CRP, IL-6 and TNF α with type 2 diabetes and IGT were also reflected by the correlation between these variables. Although both IL-6 and TNF α are known to induce the release of acute-phase proteins from hepatocytes, only IL-6 was correlated significantly with CRP ($r = 0.49$, $p < 0.0001$; Fig. 2a), but not TNF α ($r = 0.09$, $p > 0.05$; Fig. 2b).

In order to exclude confounding effects of BMI which was positively correlated with the IGT and diabetes-associated variables CRP, SAA, fibrinogen and IL-6, multivariable adjusted linear regression analyses were performed. In these analyses the association with both IGT and diabetes remained significant for CRP, SAA and IL-6, i. e. the aforementioned associations cannot merely be explained by BMI.

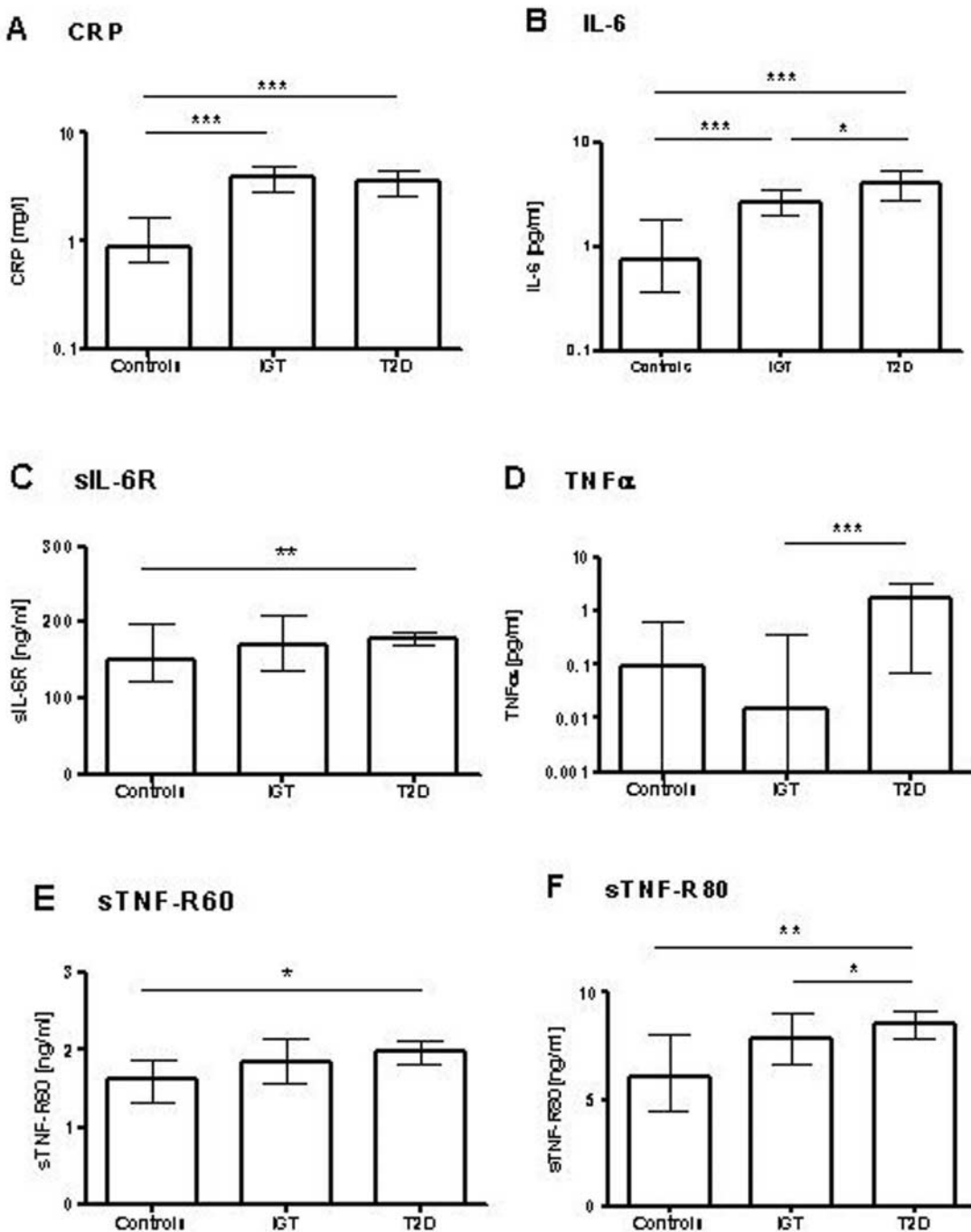


Fig. 1 Concentrations of circulating CRP (A), IL-6 (B), sIL-6R (C), TNF α (D), sTNF-R60 (E) and sTNF-R80 (F). The columns and bars represent median, first and third quartiles per group. *: $p < 0.05$; **: $p < 0.01$;

***: $p < 0.001$. Results from the KORA Augsburg Survey S4 (1999–2001).

IGT = impaired glucose tolerance; T2D = type 2 diabetes

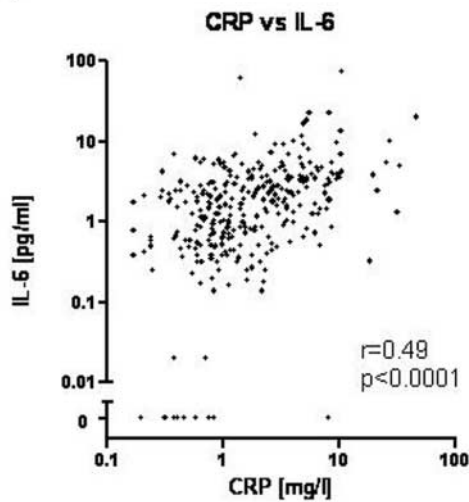
Discussion

This study based on the KORA Survey S4 yields important insights into the link between inflammation and glucose metabolism disorders. First of all, we show here that median concentrations of circulating IL-6 are significantly augmented in IGT and type 2 diabetes. The association not only with diabetes, but also with IGT suggests that IL-6 is involved in the early pathogenic events leading to diabetes manifestation and cannot merely be considered a reaction to chronic hyperglycaemia. The increase of IL-6 is paralleled by elevated levels of sIL-6R, which mediates binding to IL-6-responsive cells and therefore supports IL-6 ac-

tivity. IL-6 and sIL-6R are major components in a complex network in innate immunity which also comprises acute-phase proteins. IL-6 is known to induce CRP, SAA and fibrinogen release from hepatocytes, and our observations indeed emphasise the coordinated regulation of these immune mediators. The association of IL-6 with IGT and diabetes was mirrored by the acute-phase reactants, and their systemic levels were found highly correlated with those of IL-6 and each other. This finding underlines the biological relevance of chronically elevated IL-6 levels.

Secondly, analysis of the proinflammatory cytokine TNF α and two TNF α -antagonising soluble receptors demonstrates that

A



B

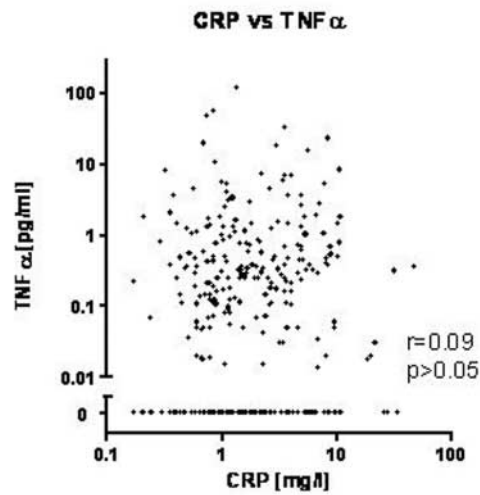


Fig. 2 Correlations of immune markers: CRP vs IL-6 (A), CRP vs TNF α (B). Each symbol represents one individual (modified after [22]). Re-

sults from the KORA Augsburg Survey S4 (1999–2001).

TNF α levels in controls did not differ from IGT and diabetes, that they were not correlated with CRP and that sTNF-R60 as well as sTNF-R80 were even slightly upregulated in diabetes. Our data therefore do neither indicate a general upregulation of inflammatory immune mediators nor a random upregulation, but rather demonstrate that IGT and diabetes are associated with a differential, specific and coordinated immune activation.

Despite the association of elevated IL-6 levels with IGT which suggests a role in diabetes development, our cross-sectional approach cannot distinguish between risk factors with pathogenic implications or risk indicators. Although in the meantime a considerable number of studies investigated the hypothesis that IL-6 could induce insulin resistance and contribute to diabetogenesis, the exact role of IL-6 remains controversial. It seems that the impact of elevated IL-6 is highly dependent on the degree of upregulation, on the immunological context and on timing [23]. Importantly, inflammation must be considered as an intricate network of stimuli, humoral and cellular proinflammatory responses, counterregulatory mechanisms and active suppression of inflammation in the absence of stimuli that do not require a potent reaction [24]. Any association of an immune mediator with IGT or diabetes might therefore, without further data, reveal a bona fide risk factor or on the contrary a mediator which participates in counterregulatory reactions and represents a protective rather than pathogenic factor.

From an evolutionary point of view, both insulin resistance and activated innate immunity have been hypothesised to have been beneficial during more than 99% of the time mankind has existed [25, 26]. In preagricultural times, hunter-gatherer lifestyle was characterised by physical activity, protein-rich and low-fat diet, periods of food shortage and above all, rampant infections, frequent injuries and low life expectancy. Individuals with a phenotype of moderate insulin resistance and activated innate immunity would have been better equipped for everyday metabolic and immunological insults. Given the physiological relevance of IL-6 in clearance of infection, tissue regeneration and wound heal-

ing, a “thrifty” genotype resulting in enhanced IL-6 responses would have been advantageous until very recently.

The “thrifty gene” hypothesis presents activated innate immunity and insulin resistance as two sides of a coin, but cannot resolve the question of how these two sides are linked. Several studies indicate that cytokines and other immune markers could be considered as mediators between environmental and lifestyle factors (high caloric diet, physical inactivity) and “traditional” risk (hyperglycaemia, dyslipidaemia, obesity) on the one hand and insulin resistance and β -cell failure on the other hand. Although sound evidence from clinical trials is still lacking, animal studies show that disruption of immune genes like TNF α , plasminogen activator inhibitor (PAI)-1 or intercellular adhesion molecule (ICAM)-1 significantly modulates the diabetogenic potential of high calorie diets [27–29]. Furthermore, cytokines such as IL-6 or TNF α can directly interfere with insulin signalling or indirectly interact with adipocytes, neuronal or other cells [9, 30–33]. In this context, it is also important that complementary studies will be required to address the problem whether the subclinical inflammation seen in IGT and type 2 diabetes is “inflammatory” (i. e., nonspecifically caused by metabolically stressed cells) or antigen-driven. Damaged or stressed cells release antigens like heat-shock proteins such as hsp60 and oxidised lipids which can cause or maintain disease processes [34–36]. Despite the wealth of information about the involvement of the immune system in the development of diabetes, many interactions remain to be unravelled. The design of specific and effective strategies to prevent type 2 diabetes in particular in patients in which lifestyle changes do not suffice will not be possible until we understand the aforementioned issues much better than today.

Outlook

The analysis of samples from the KORA Survey S4 is currently being extended to chemokines, a group of low-molecular proteins which have been described as important components of in-

nate immune reactivity, but has not been investigated in the context of type 2 diabetes. Chemokines represent a family of small molecular weight proteins which control leukocyte trafficking and activation and act as key mediators of inflammation and other patho-physiological states [37, 38]. They are also involved in features of the metabolic syndrome and are thus of particular interest in the context of type 2 diabetes.

Current projects also focus on the link of inflammation and obesity as prominent risk factor of type 2 diabetes. Recent studies indicated that obesity is associated with an increasing infiltration of macrophages into adipose tissue [39–41]. The analysis of the association of immune mediators with obesity parameters should help to elucidate the contribution of adipose tissue to diabetes-related inflammation.

All projects are complemented by genetic investigations ([50]) to further define immunity-related risk indicators and risk factors for type 2 diabetes. The overall aims of the KORA S4-based collaboration are (i) to gain more information about the causal role of immune mediators in diabetogenesis and about their potential as therapeutic targets and (ii) to answer the question whether determining a pattern of immune markers (circulating proteins and immune variants) in addition to traditional risk factors might be helpful to identify those at high risk of developing type 2 diabetes in order to reduce the incidence of diabetes-related complications with high morbidity and mortality.

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