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Chapter 3

Type 2 Diabetes, Immunity and Cardiovascular Risk: A Complex Relationship

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Additional information is available at the end of the chapter

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1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997, 2003)

2. Epidemiology

Diabetes is one of the most common chronic diseases in the world. It is thought that more than 360 million persons will be affected by this disease in 2030 (Wild et al., 2004). Prevalence of diabetes is higher in western countries because of the increasing of population age, physical inactivity and obesity, however it is rapidly spreading also in developing countries due to the socio-economic growth with progressive urbanization and changes in lifestyle.

Cardiovascular disease (CVD) in diabetic patients is characterized by microvascular damage, associated with the development of diabetic retinopathy, nephropathy, and neuropathy, and macrovascular complications linked to the accelerated course of atherosclerosis shown in these patients. Coronary heart disease (CHD) remains the principal cause of morbidity and mortality, in association with an increased risk of developing cerebrovascular disease, peripheral vascular disease and heart failure.

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3. Classification and pathogenesis (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997)

DM is classified on the basis of pathogenetic mechanisms leading to hyperglycemia:

- Type 1, due to a virtually complete lack of endogenous pancreatic insulin production caused by an immune-mediated destruction of pancreatic beta cells (Immunomediated Type I diabetes), or by unknown mechanisms (Idiopatic Type I diabetes);
- Type 2, accounting for ~90–95% of diabetic patients. Its complex pathogenesis, resulting from a combination of genetic predisposition, unhealthy diet, physical inactivity, and increasing weight with a central distribution of the adipose tissue leads to insulin resistance and usually relative (rather than absolute) insulin deficiency;
- Other specific types of diabetes, related to genetic defects of insulin secretion and/or action in peripheral tissues, endocrinophaties, or infections;
- Gestational DM.

Immune system and autoimmunity play a pivotal role in the pathogenesis of type 1 diabetes mellitus (T1DM) (Atkinson & Maclaren, 1994), however inflammation may play a crucial intermediary role also in type 2 diabetes mellitus (T2DM) (Mykkänen, 2000) and in the development of its complications, including cardiovascular disease, thus linking it with several coexisting conditions thought to originate through inflammatory mechanisms.

4. Inflammation, diabetes and cardiovascular risk

Epidemiological studies conducted at the end of 1970 described diabetes as a major independent risk factor for cardiovascular disease, causing 2-4 folds increase in cardiovascular risk (Kannel & McGee, 1979). Atherosclerosis is responsible for the 80% of deaths in diabetic patients (Gu K et al., 1998)[7], and diabetes is considered a "coronary disease equivalent", since several studies pointed out that diabetes-associated CV risk is similar to that observed among non-diabetic patients with prior myocardial infarction (MI) (Haffner et al., 1998; Schramm et al., 2008).

Diabetes is associated with an increased risk of MI and affects more than 30% of patients with acute coronary syndromes (ACS) (Fang & Alderman, 2006). Diabetic patients show a worse outcome after ACS events (Malmberg et al., 2000; Murcia et al., 2004), a more complicated course of the disease and a higher incidence of ischemic recurrences (Cantrill et al., 1995; Miettinem et al., 1998; Shindler et al., 2000). Moreover, if undergoing revascularization procedures, they have a worse prognosis than patients without diabetes (Banning et al., 2010; Hlatky et al., 2009).

Several angiographic studies highlighted a greater spread and progression of atherosclerotic disease in diabetes patients. Moreover, histological specimens of atherosclerotic plaques obtained in diabetic patients exhibit larger lipid core, a higher inflammatory cell infiltration and increased neovascularization (Burke et al., 2004; Moreno & Fuster, 2004).

Since the isolated treatment of hyperglycemia has not been associated to a reduction of CV risk in diabetic people, more aggressive primary and secondary prevention measures are needed in these patients (ADVANCE Collaborative Group, 2008; UKPDS Group, 1998).

The early onset and the burden of macroangiopathy in diabetic patients have a multifactorial pathogenesis and are the result of very complex mechanisms including the coexistence of multiple risk factors, such as obesity, hypertension and dyslipidemia. Moreover hyperglycemia, insulin resistance, hyperinsulinemia and the presence of Advanced Glycation End-products (AGE) in plasma and vascular wall are all mechanisms involved in the establishment of a pro-inflammatory state characterized by the activation of inflammatory cells and cytokine production, leading to immune dysregulation and pro-thrombotic state.

On the other hand, inflammation can be considered a common link between these factors, being involved in each step of atherothrombosis, from the formation to the complications of the plaque, and in the metabolic dysregulation characterizing diabetes.

Several studies have demonstrated a correlation between T2DM, inflammation and innate immunity system. These evidences, together with more recent findings on inflammation and immune mechanisms, could pave the way to a new etiopathogenic hypothesis of Metabolic Syndrome and T2DM, firstly proposed by Pickup in 1997 (Pickup, 2004), and suggesting that activation of innate immunity, together with a chronic inflammatory response, could also play a pivotal and early role in *causing* diabetes, instead of being a mere *consequence* of hyperglycemia, hyperinsulinemia and obesity.

Recent evidences have also shown that adaptive immunity and autoreactivity could play a role in the pathogenesis of T2DM and in its complications (Figure 1).

5. Diabetes and innate immunity

5.1. Systemic markers of inflammation

Established T2DM is associated with elevated circulating biomarkers of innate immunity activation, including C-reactive protein (CRP) and interleukin (IL)-6 and these alterations are also present in patients with pre-diabetes and metabolic syndrome. In fact several cross-sectional studies in non-diabetic subjects, in the general population (Festa et al., 2000; Ford, 1999a, 1999b; Frohlich et al., 2000; Hak et al., 2001; Sakkinen et al., 2000; Yudkin et al., 1999; Visser et al., 1999; Weyer et al., 2002)[23-31], or in individuals with impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) (Muller et al. 2002;, 2002b, Sriharan et al., 2002), have confirmed that acute-phase reactants are positively correlated with measures of insulin resistance, plasma insulin concentration, BMI, waist circumference, and circulating triglyceride, and negatively correlated with HDL cholesterol concentration.

Additional cross-sectional studies in newly diagnosed (Temelkova-Kurktschiev et al., 2002) or established T2DM patients (Arnalich et al., 2000; Leinonen et al., 2003; Richarsdon & Tayek, 2002; Rodriguez-Moran & Guerrero-Romero, 1999) have confirmed that acute-phase

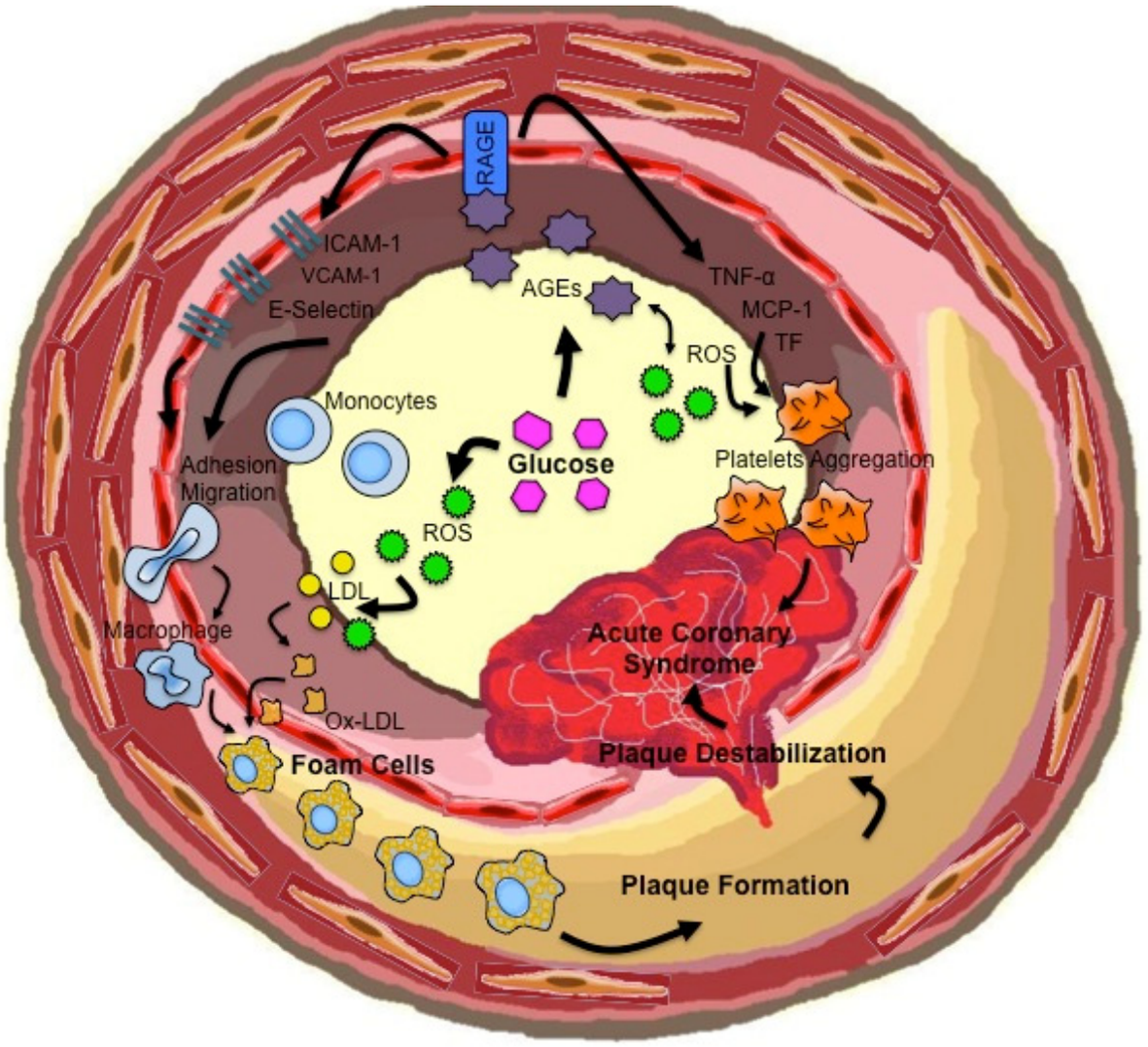

Figure 1. Schematic representation of the principal mechanisms linking diabetes, vascular injury and atherosclerotic disease. Hyperglycemia induces formation of advanced glycation end products (AGEs) that bind to their receptors (RAGE) present on endothelial cells, smooth muscle cells, monocytes and macrophages, thus promoting vascular inflammation, endothelial dysfunction, and prothrombotic state. Hyperglycemia and AGEs also cause generation of reactive oxygen species (ROS), which in turn increase AGE and oxidized low-density lipoproteins (ox-LDL) formation. These pathways are all involved in the development of atherosclerosis and plaque progression/destabilization in diabetic patients.

markers such as CRP and IL-6 are elevated in these subjects compared with non-diabetic controls (Katsuki et al., 1998; Pickup et al., 2000; Winkler et al., 1998).

On the other side it has been shown how abnormal circulating levels of acute-phase reactants, in particular CRP and serum amyloid A, and inflammatory cytokines like IL-6, are good predictor of the development of T2DM in nondiabetic subjects. Schmidt and colleagues (Duncan et al., 1999; Schmidt et al., 1999), using data from the Atherosclerosis Risk in Communities study, showed for the first time that inflammatory markers, such as white blood cell count, low serum albumin, α1-acid glycoprotein, fibrinogen, and sialic acid,

predict the development of T2DM and this has been confirmed by several follow-up studies in different populations (Table 1).

Authors	Year	Inflammatory marker(s) analized	Subjects	Follow-up (years)
Pradhan et al.	2001	CRP and IL-6	US women	4
Barzilay et al.	2001	CRP	US men and women	3-4
Vozarova et al.	2002	White blood count	Pima Indians	5,5
Festa et al.	2002	CRP, fibrinogen, and PAI-1	Multiethnic subjects	5
Freeman et al.	2002	CRP	Scottish men	5
Ford et al.	2002	White blood count	US men and women	20
Nakanishi et al.	2002	White blood count	Japanese men	6
Snijder et al.	2001	CRP	Dutch men and women	6
Spranger et al.	2003	IL-6, with additional risk of IL-6 and IL-1 combined	German men and women	2.3
Thorand et al.	2003	CRP	German middle-aged men and women	7.2

Legend: CRP, C-reactive protein; IL, interleukin; PAI, plasminogen activator inhibitor.

Table 1. Inflammatory markers and the prediction of T2DM development

The association between altered levels of acute-phase reactants and the development of diabetes is generally independent of age, sex, blood glucose concentration, family history of diabetes, physical activity, smoking, and baseline atherosclerosis, while it seems to be weaker if adjusted for obesity (Pickup, 2004).

It has been shown that treatment with high doses of aspirin is associated with a 25% reduction in fasting plasma glucose, a 50% reduction in triglycerides and a 15% decrease of total cholesterol and CRP, even if no change in body weight occurs (Hundal et al., 2002).

Recent studies have shown a role played by genetic variations in influencing the innate immune response and the risk of developing T2DM, obesity and atherosclerosis (Fernandez-Real & Pickup, 2008). These variations can relate to genes encoding proteins like inflammatory markers, cytokines and cellular pattern-recognition receptors (PRR).

Genetic predisposition to high transcription rate of TNF-α and IL-6 genes is associated with an increased risk of developing obesity, insulin-resistance and diabetes (Fernandez-Real & Ricart, 2003).

Increased levels of inflammatory markers and insulin resistance have been also connected to a genetically determined reduction of serum levels of soluble CD14, a molecule expressed by macrophages able to bind lipopolysaccharide (LPS), and Bactericidal and Permeability Increasing protein (BPI), produced by neutrophils (Fernandez-Real et al., 2003; Gubern, 2006).

Moreover, decreased levels of mannose-binding lectine (MBL), a protein involved in the clearance of infectious pathogens through the induction of complement activation and macrophage phagocytosis, have been associated both with a raised risk of infections (Summerfield et al., 1997), CHD (Best et al., 2004), obesity and insulin resistance (Fernandez-Real et al, 2006).

5.2. Toll like receptors as link between inflammation and metabolic diseases

Mechanisms by which the activation of the innate immunity can cause insulin resistance have been clarified recently; many studies have revealed how TNF-α could activate the c-Jun NH2-terminal kinase, a stress-induced kinase which serinephosphorylates many signaling proteins, including insulin receptor substrate (IRS)-1 and IRS-2, thereby inhibiting insulin signaling (Morris et al., 2003).

A crucial role, in this setting, is probably played by Toll-like receptors (TLR). TLR are key receptors of innate immunity recognizing a huge number of molecules usually expressed by pathogen microorganisms but absent in mammal tissues, named pathogen-associated molecular patterns (PAMPs), and other molecules called damage-activated molecular patterns (DAMPs); therefore TLR belong to the family of PRR (Kawai & Akira, 2010).

To date, 13 TLRs have been described, both located on the extracellular surface or in the intracellular compartment (Takeda & Akira, 2004). Among them, TLR2 and TLR4 have been associated with metabolic disorders, as well as with atherosclerosis and its clinical manifestations. TLR2 and TLR4 loss-of-function, absence or inhibition in high-fat diet murine models has been related to a decrease in weight gain, insulin resistance and beta-cells dysfunction (Caricilli et al., 2008; Ehses et al., 2010; Tsukumo et al., 2007). TLR4 is highly conserved and selectively activated by lipopolysaccharides (LPS), a constituent of Gram-negative bacterial cell-wall (Kawai & Akira, 2010). Some authors have demonstrated how the lauric acid, a medium-chain fatty acid (FA) component of LPS, trigger TLR4 signaling in macrophages and have revealed how saturated FAs, but not unsaturated, activate inflammatory signals in adipose cells and macrophages (Lee et al., 2001, 2003). Other studies have proposed that the sphingolipid ceramide, synthesized from FAs, might represent a possible link between high-fat diet intake and TLR pathways. Indeed, sphingolipid ceramide is able to activate TLR4 signaling (Fischer et al., 2007; Schwartz et al, 2010), and the inibition of its biosynthesis improves glucose tolerance in murine models

(Holland et al., 2007). However, the previously described studies have not adequately eliminated potential contamination of the reagents used in the experimental condition with bacterial products. Therefore, the direct stimulation of TLRs in various cell types attributed to saturated FAs might be due to LPS contamination (Erridge & Samani, 2009).

The expression in the vessel wall of both TLR2 and TLR4 has a synergistic effect on the progression of atherosclerotic plaque (Monaco et al., 2009; Shinoara et al., 2007). TLR4, whose endogenous ligand is ox-LDL (Xu et al., 2001), is highly expressed in SMC of atherosclerotic vessels, where it has been associated with the induction of a pro-inflammatory phenotype (Loppnow et al., 2008; Otsui et al., 2007). Furthermore, TLR4 has been found in atherosclerotic lesions and at the site of plaque rupture in patients with MI (Ishikawa et al., 2008), and its expression is increased in thrombi from patients with acute coronary syndromes (Wyss et al., 2010; Yonekawa et al., 2011). Moreover, several studies showed that circulating monocytes of patients with atherosclerotic disease exhibit higher expression of TLR2 and TLR4 as compared to healthy individuals (Geng et al., 2006; Kuwahata et al., 2010; Mizoguchi et al., 2007; Shiraki et al., 2006), and an enhanced TLR signaling has been demonstrated in monocytes of patients with ACS (Ashida et al., 2005; Methe et al., 2005; Versteeg et al., 2008).

To date, the mechanisms linking high-fat diets with TLR-signaling and associated pathologies, such as atherosclerosis and insulin resistance, remain to be discovered. As an alternative TLR-dependent mechanism, currently under investigation, the large quantities of lipopeptide and LPS derived from the commensal organisms of the mammalian intestine may contribute to systemic stimulation of TLR2 or TLR4 signaling. Administration of LPS in mice has been associated with an increase of hepatic insulin resistance and a decrease of glucose tolerance (Arkan et al., 2005; Cani et al., 2007). It has been shown that blood levels of LPS are higher in T2DM patients than in healthy controls and correlate with insulin levels and glucose (Al-Attas et al., 2009; Creely et al., 2007; Harte et al., 2010). Hence, an increased level of PAMPs like LPS may play an important role in the development of the inflammatory status characterizing metabolic diseases like T2DM.

Main sources of PAMPs are represented by infections, commensals and diet (Erridge, 2011). It's difficult to assess the quantitative contribution of each of them to PAMPs burden in humans, but increasing evidences are demonstrating that, under certain conditions like high fat meals, PAMPs derived from commensals and diet can effectively translocate from the intestinal lumen to the circulation (Erridge et al, 2007; Laugerette et al., 2010). Indeed, it has been widely demonstrated that oral microorganisms and human periodontitis are associated with an increased risk of developing atherosclerosis and T2DM (Bahekar et al., 2007). The small intestine seems to be the main contributor of the global circulating PAMPs burden, mostly due to the absorption of PAMPs swallowed from the oral cavity. This is probably due to the bigger surface area compared to large intestine and the fat-soluble nature of PAMPs such as LPS, accounting for their easier absorption in chylomicrons with dietary fat, a process taking place only in the small intestine (Ghoshal et al., 2009). Moreover, it is reasonable that the most part of PAMPs absorbed in the large intestine firstly reach liver through the portal system, being there effectively removed from circulation; on the other

hand, PAMPs from the small intestine, through chylomicrons absorption, can reach lymphatic system and general circulation bypassing the liver. Finally a quote of PAMPs may come from diet. Interestingly, it has been demonstrated that PAMPs are nearly absent in fresh food, but they can be copious in a number of processed food typical of Western diet, such as meat and dairy products (Erridge, 2010, 2011).

5.3. Role of inflammasomes in peripheral insulin resistance

Recent studies also highlighted a crucial role of inflammasomes pathways both in insulin production and in insulin sensitivity.

Inflammasomes are group of protein complexes which recognize a diverse set of inflammation-inducing stimuli, including PAMPs, and DAMPs (Strowig et al., 2012). The activation of these complexes lead to the proteolitic activation of caspase-1 and, finally, to the production and release of important pro-inflammatory cytokines such as IL-1β and IL-18 (Davis et al., 2011; Schroder & Tschopp, 2010). The most widely studied inflammasome is the NLRP3 inflammasome, which could be activated by a large variety of signals, included PAMPs, DAMPs and bacterial toxins.

A two-step process is required to induce NLRP3 inflammasome activation. A first priming step is usually mediated by PRRs, such as TLR, or cytokines receptors known to induce activation of NFkB, and leads to production and intracellular release of inactive forms of NLRP3. A subsequent activation step induces the inflammasome assembly; it starts in response to a variety of stimuli, such as potassium efflux, extracellular ATP, reactive oxygen species (ROS) and rupture of lysosomal membrane integrity, and leads to caspase-1 activation and cleavage of pro-IL1β. Recent evidences suggest that NLRP3 play a pivotal role both in the early stages and in the chronic progression of T2DM (Kahn et al., 2006). Vandanmagsar et al. found that NLRP3 inflammasome is largely expressed in adipose-tissue-infiltrating macrophages, and it is activated by obesity–associated 'danger–signals', such as the saturated fatty acid palmitate and lipotoxicity–associated ceramide (Vandanmagscar et al., 2011). They also demonstrated how the expression of NLPR3 in the adipose tissue is directly correlated to insulin resistance both in mice and humans and that blockade of NLRP3 could reduce inflammation and improve insulin sensitivity (Vandanmagscar et al., 2011). Other studies demonstrated that during obesity, circulating free fatty acids are scavenged by adipose tissue macrophages to produce ceramide (Shah et al., 2008) and confirmed the role of this lipid molecule in inducing NLRP3 inflammasome activation (Boden & Ceramide, 2008). IL-1β, produced as a result of inflammasome activation, inhibits insulin signaling (Wen et al., 2011) by direct serine phosphorylation of IRS-1 and induces the expression of TNF-α (Strowig et al, 2012), an insulin-resistance-promoting cytokine as discussed above. IL-1β and IL-18 also induce type 1 $CD4^+$T-helper cells differentiation in adipose tissue (Vandanmagscar et al., 2011). Moreover, the activation of caspase-1 seems to be related also to adipocytes differentiation and adipokines production (Stienstra et al., 2011).

Inflammasome activation is also involved in impaired insulin secretion associated with overt T2DM. Human β-cells are capable to produce IL-1β when exposed to elevated glucose

concentration (Maedler et al., 2002). Several models have been proposed to explain the inflammasome mediated pancreatic islets dysfunction and particularly the role of ROS induced inflammasome activation has been highlighted. Hyperglycemia stimulates mitochondrial ROS production by increasing the activity of the electron transport chain, leading to the activation of NLRP3. Thioredoxin-interacting protein (TXNIP) is usually bound to oxidoreductase thioredoxin, however, when intracellular ROS increase, it seems to act as an upstream specific activating lingand for NLRP3. TXNIP expression is induced by glucose (Oka et al., 2009) and repressed by insulin (Parikh et al., 2007). Moreover, glucose induces the expression of TXNIP in pancreatic islets but not in macrophages(Zhou et al., 2010) and glucose dependent IL-1β secretion in pancreatic islets is inhibited in TXNIP- and NLRP3-knockout mice and antagonized by ROS-blockers. Taken together, these evidences suggest that a chronic condition of high plasmatic glucose levels induces pancreatic islets dysfunction through a mechanisms involving TXNIP-dependent NLRP3 inflammasome and that, once activated, this inflammasome could represent an adjunctive and self-maintaining immune-metabolic stressor.

Hystopathological studies recently showed deposition of islet amyloid polypeptide (IAPP, also known as amylin) in pancreatic islets of T2DM patients (Seino et al., 2001), that seems to be able to specifically activate the NLRP3 inflammasome through a mechanism that involves disruption of the phagolysosomal pathway (Masters et al., 2010).

Additional support for a pathological role of inflammasomes in T2DM comes from human clinical trials in which blockade of IL-1β signaling by Anakinra, a recombinant human IL-1 receptor antagonist (IL-1RA) demonstrated sustained reduction of inflammation, improved glycaemic control and β-cell function in T2DM patients (Dinarello et al., 2010; Larsen et al., 2007).

Moreover inflammatory cytokines such as TNF-α, IL-1β, and IL-6 also downregulate peroxisome proliferator activated receptor-γ (PPAR-γ) expression (Tanaka et al., 1999). PPAR-γ is a ligand-activated transcription factor highly expressed in adipose tissue, where it controls adipocyte differentiation and lipid storage, and modulates insulin action. It represents the target of thiazolidinediones (TZDs) pioglitazone and rosiglitazone, which are demonstrated to improve glycemic control and insulin-sensitivity and to reduce T2DM-associated inflammation (Miyazaki et al., 2001a, 2001b)[120,121].

As noted above, much evidence suggests an intimate relationship among IL-1β, the NLRP3 inflammasome and the metabolism of lipids and carbohydrates. This occurs at the level of enhanced NLRP3 inflammasome activation and processing of IL-1β to the mature cytokine in response to saturated fatty acids and also at the level of glucose metabolism through the requirement of glycolysis for induction of IL-1β mRNA. The pathogenic role of IL-1β in atherosclerotic plaque formation and in insulin resistance in T2DM attests to the importance of inflammasome-mediated pathways as link between inflammation, T2DM and CVD. The exacerbation of NLRP3 inflammasome activation by cholesterol crystals in atherosclerosis (Duewell et al., 2010; Rajamäki et al, 2010) and by IAPP in type 2 diabetes (Masters et al., 2010), provides a positive feedback loop to promote disease pathogenesis.

Taken together, these findings support a crucial role of different molecules and pathways of innate immunity in the complex metabolic imbalance underlining T2DM, and possible contributing to the disease-associated cardiovascular risk. Insight into the above described molecular pathways could help in the design of new therapeutic strategies.

6. Diabetes and adaptive immunity

In the past years, a possible role of adaptive immunity and autoreactive mechanisms in the pathogenesis of T2DM has probably been underestimated and, therefore, poorly investigated. However, increasing evidences support the role of autoimmunity and adaptive immune system in the pathogenesis of T2DM and its vascular complications (Brooks-Worrell & Palmer, 2012; Nikolajczyk et al, 2011). It has been recently demonstrated that T-lymphocytes of patients with T2DM produce large amounts of pro-inflammatory cytokines, such as IL-8, showing in contrast a decreased production of anti-inflammatory cytokines, such as IL-10 (Jagannathan et al., 2010). These functional alterations are consistent with those previously demonstrated in monocytes of T2DM patients (Giulietti et al., 2007; Hatanaka et al., 2006; Pitocco et al., 2009), and result in an imbalance of cytokines network and in a strongly pro-inflammatory environment. High pro-inflammatory cytokines production has been associated in several studies with insulin-resistance and DM development, while the inhibition of some pro-inflammatory mediators prevented insulin-resistance in mice (Arkan et al., 2005; Cai et al., 2005; de Roos et al., 2009; Ehses et al., 2009; Reimers, 1998.

Moreover, the role of a perturbation of T-cell repertoire has been demonstrated in murine models of T2DM. Particularly, regulatory T-cells (Treg) are significantly diminished in the adipose tissue of obese insulin-resistant mice compared to non-obese animals. Treg cells isolated and expanded ex-vivo, in these models, were found able to exert an anti-inflammatory activity and lessen insulin-resistance (Feuerer et al., 2009). On the other hand, Interferon (IFN)-γ-producing cells in the adipose tissue of obese mice may cause an imbalance in glucose homeostasis. The alterations mediated by T-cells with a Th1 phenotype, characterized by IFN- γ production, can be counterbalanced by $CD4^+$T-cells with an anti-inflammatory phenotype, such as Treg and Th2 lymphocytes producing IL-10 (Winer et al., 2009), thus underlining the importance of a physiological balance between different T-cells subset in the metabolic homeostasis of adipose tissue, which has a crucial role in the pathogenesis of insulin resistance and T2DM onset. Another cellular type possibly involved in inflammation and insulin-resistance in T2DM are IL-17 producing T-cells, so called Th17. This aggressive, pro-inflammatory T-cell subset has been found at high levels following IL-6 stimulation in the spleen of obese mice, and could contribute to the inflammatory environment strongly related to insulin resistance development and maintenance in T2DM (Winer et al., 2009). Consistently with this hypothesis, high levels of cytokines conditioning T-cell differentiation toward a Th17 phenotype, such as IL-6, IL-1β and Tranforming Growth Factor (TGF)-β, have been measured in diabetic patients (Acosta-Rodriguez et al., 2007; Andriankaja et., 2009; Osborn et al., 2008; Yang et al., 2008). These pro-inflammatory cytokines could promote Th17 cells expansion and inhibit Treg

differentiation in T2DM patients. In recent years, a higher percentage of a particular T-cell type, $CD4^+$ $CD28^{null}$ T lymphocytes, has been found in diabetic patients undergoing microvascular complications, e.g. proliferative retinopathy (Canton et al., 2004). An expansion of this particular T-cell population, which is infrequent in healthy young people and slightly expanded in the elderly, has been detected in patients with unstable angina (Liuzzo et al., 1999, 2000); in this population, a percentage of $CD4^+CD28^{null}$ T-cells >4%, representing the 90^{th} percentile of distribution in healthy individuals, is associated with a poor outcome (Liuzzo et al., 2007). These cells have particular aggressive features, showing an increased IFN-γ production and anti-apoptotic factors expression (Liuzzo et al., 2001), and could be involved in abrupt atherosclerotic plaque destabilization through several mechanisms. In fact, $CD4^+CD28^{null}$ T-lymphocytes exert cytolitic effects on endothelial cells and express high levels of TNF-related apoptosis-inducing ligand (TRAIL), thus promoting smooth muscle cells apoptosis within the atherosclerotic plaque (Nakajima et al., 2002; Sato et al., 2006). With these premises, the recent finding of an expansion of $CD4^+$ $CD28^{null}$ T-cells in diabetic patients is extremely interesting, suggesting a possible role of adaptive immune disregulation, either primary or induced by the altered metabolic status and the inflammatory environment characterizing the disease, in the increased cardiovascular risk which is one of the most relevant clinical features of T2DM, accounting for the majority of disease-related mortality and morbidity (Giubilato et al., 2011). Consistently, in the same study $CD4^+$ $CD28^{null}$ T-lymphocytes expansion was closely related to a poor glycaemic control, and was associated with a higher incidence of cardiovascular events during follow-up.

Other fingerprints of adaptive immunity activation have been investigated in T2DM patients.

Increased activity of adenosine-deaminase (ADA) has been described in this population (Prakash et al., 2006). ADA is an enzyme that converts adenosine into inosine through an irreversible deamination reaction, and it is involved in T-cell proliferation and activation (Kather, 1990). Moreover, since adenosine increases glucose uptake into cells, an effect of ADA in reducing tissutal insulin sensitivity has been described (Gorrell et al., 2001). A recent study has confirmed an increased ADA activity in T2DM patients, underlining also an association between enzyme function and fasting glucose levels, as well as HbA1c. Thus, inflammation, T-lymphocytes activation and glucose metabolism seem to be tightly related in the complex setting of T2DM (Lee et al., 2011).

Tregs are another important T-cell type widely involved in autoreactive processes and in the modulation of the inflammatory environment associated with various diseases and pathological conditions. In the setting of diabetes mellitus, Tregs have been extensively investigated both in animal models and human patients with T1DM (Chatenoud et al., 2005, Randolph & Fathman, 2006), while less studies have been performed on Tregs in T2DM. Interestingly, a recent study in mice demonstrated that Treg induction was associated to a reduction of adipose tissue inflammation and insulin resistance, with a concomitant improvement of metabolic parameters of lipid metabolism and glycaemic control (Ilan et al, 2010). Consistently, a subsequent study proved an inverse relation between Treg expression

and function and insulin resistance in mice; Treg expansion was also associated with a reduction of signs of diabetes-related end-organ damage, such as nephropathy (Eller et al, 2011).

Finally, B-lymphocytes function has been poorly investigated in T2DM, but some data seem to indicate a role of these cells in the establishment and/or maintenance of a chronic proinflammatory state in this setting. For example, an altered B-cell activity related to cellular TLR dysfunction and leading to increased IL-8 and decreased IL-10 production has been recently demonstrated (Jagannathan et al, 2010).

Overall, these evidences suggest a diabetes-associated alteration of all components of adaptive immunity; these alterations could be implicated in the pathogenesis of the disease and, on the other hand, triggered and maintained by the disease itself, thus creating a pro-inflammatory, pro-atherosclerotic, vascular-damaging environment strongly associated with cardiovascular complications of T2DM.

7. Treating T2DM by targeting immunity

As a role of inflammation has been suggested in the development of diabetes and its vascular complications, TLRs and inflammasome could represent attractive drug targets. Several drugs currently adopted to control hyperglycemia and inflammation and improve prognosis in T2DM patients may also exert their effects on TLR-mediated pathways. For example, it has been shown that statin therapy reduces TLR2 and TLR4 expression (Methe et al., 2005; Niessner et al., 2006; Stoll et al., 2006). The role of PPAR-γ agonists in inhibiting TLR activation both in vitro and in vivo has also been investigated (Dasu et al., 2009; Ji et al., 2009), as well as the ability of some angiotensin receptor blockers to decrease mRNA and protein levels of TLR2 and TLR4 (Dasu et al., 2009). However, although several molecules and drugs could potentially reduce inflammation associated with TLR signaling, studies on humans have to date shown a clear beneficial effect only related to statin therapy. Moreover, no drugs directly targeting TLRs have been developed.

For what concerns inflammasome's related pathways, the role of IL-1β in the impairment of pancreatic β -cell function, leading to apoptosis and decompensated insulin secretion, has prompted the use of anakinra in a double-blind clinical trial in patients with T2DM, that showed an improvement in β -cell secretory function, glycemia and inflammatory markers both during treatment and after drug withdrawal (Larsen et al., 2007, 2009).

A recent study tested in mice the efficacy of a high affinity monoclonal antibody to IL-1β, XOMA 052, showing an inhibition of atherosclerotic plaques formation (Bhaskar et al., 2011). Although clinical trials testing this antibody in T2DM patients failed in demonstrating an improvement in glycemic control, XOMA 052 potentially might reduce cardiovascular risk, since its administration in diabetic patients was associated with a reduction of inflammatory markers and increased levels of high-density lipoprotein.

Furthermore, drugs directly targeting caspase-1 have been tested in mice with promising results in reducing obesity and improving insulin sensitivity (Stienstra et al., 2010).

8. Conclusions

Type 2 diabetes is a complex disease involving the whole metabolic profile of the organism and exerting pathological effects on several organs and systems. The disease is associated with a chronic low-grade inflammation predictive of, and possibly responsible for, many of the clinical signs and complications of T2DM. The diabetes-associated inflammatory status can be the consequence of the metabolic abnormalities characterizing the disease, but increasing evidences are proposing also an important role of immune system disregulation, involving both innate and adaptive immunity, in the pathogenesis of T2DM. Cellular homeostasis is strictly dependent on the cross talk between immune system and metabolic regulators. Hence, any imbalances between them could represent a trigger for metabolic dysfunctions such those related to diabetes. Despite the huge number of evidences at our disposal highlighting the role of TLRs' and inflammasomes' pathways in pancreatic islets dysfunction and T2DM, to date no drugs directly targeting TLRs or the NLRP3 inflammasome have been developed. However, clinical trials have been addressed, with positive results, at evaluating the efficacy of downstream products' blockers, such as Anakinra, a recombinant IL-1RA.

Further studies are warranted in unraveling the complex relationship between T2DM and immune system, and its implication for cardiovascular diseases.

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