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Autoimmunity and Immunotherapy of Type 1 Diabetes

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1. Introduction

Type 1 diabetes, formerly termed insulin-dependent diabetes mellitus (IDDM), is a chronic organ-specific autoimmune disorder thought to be caused by proinflammatory autoreactive CD4+ and CD8+ T cells, which mediate progressive and selective damage of insulin-producing pancreatic beta-cells (Atkinson & Eisenbarth, 2001). The reduction of beta-cell mass leads to a lack of insulin and thereby loss of blood glucose control (Boettler & von Herrath, 2010).

The worldwide prevalence of T1D was estimated to be 171 million cases among the adult population (Wild et al., 2004). Its annual incidence varies widely from one country to another (from less than 1 per 100,000 inhabitants in Asia to approximately up to 25/100,000 population/year in North America, more than 30 per 100,000 in Scandinavia and up to 41/100,000 population/year in Europe). It is in steady increase across the globe, especially among children aged less than five years (Kajander et al., 2000; Vija et al., 2009).

According to the European Diabetes (EURODIAB) study group, the prevalence of T1D in Europe will increase significantly in children younger than 15 years of age to reach 160,000 cases in 2020 (Patterson et al., 2009). These data will result in an increasing number of patients with longstanding diabetes and with a risk of serious complications (Kessler, 2010). These include heart diseases and strokes, high blood pressure, renal failure and ketoacidosis (DKA) (Boettler & von Herrath, 2010).

To date, it has not been possible to prevent the autoimmune response to beta-cells in human, due probably to its unknown aetiology, although it is known that development of T1D is genetically controlled and thought to be initiated in susceptible individuals by environmental factors such as virus infections (Luo et al., 2010; Mukherjee & DiLorenzo, 2010; von Herrath, 2009).

It is now evident that targeted destruction may go undetected for many years, but antibodies to various beta-cell antigens can be easily demonstrable in the sera of patients at risk before clinical onset (Achenbach et al., 2005). Additionally, some endogenous insulin secretion is generally present at the onset of clinical diabetes (Scheen, 2004), during which time, immunotherapeutic intervention may be effective (Staeva-Vieira et al., 2007).

This chapter emphasizes the principal immunological risk markers of T1D and especially the role of cell-mediated immune response leading to pancreatic beta-cells destruction, as well as the most promising immunotherapeutic approaches for prevention and treatment of the disease.

2. Autoimmunity of the type 1 diabetes

The autoimmune nature of T1D is initially affirmed by several arguments that are primarily indirect, including the association with other autoimmune diseases (Barker, 2006), such as the autoimmune thyroid disease (Hashimoto thyroiditis or Graves disease) (Criswell et al., 2005; Levin et al., 2004), Addison disease (Barker et al., 2005), myasthenia or Biermer's anemia, and the detection of various autoantibodies (Seyfert-Margolis et al., 2006) and islet lymphocytes infiltrates (Bach, 1979).

2.1 Humoral markers of type 1 diabetes

Although T1D is primarily mediated by mononuclear cells (Carel et al., 1999), diagnosis means of the preclinical period are primarily markers of humoral immune response that are represented, for instance, by antibodies to beta-cell antigens, including glutamic acid decarboxylase 65, insulin, insulinoma-associated protein 2 islet tyrosine phosphatase, islet cell cytoplasm and more recently zinc transporter 8 (Luo et al., 2010) (Fig. 1). Studies of twins or in subjects with a family history of autoimmune diabetes have shown that these markers, when associated in the same subject, confer very high risk of developing diabetes within 5 years (Verge et al., 1996). The predictive value increases from less than 5% in the absence of antibodies to more than 90% when antibodies to GAD, tyrosine phosphatase IA-2 and insulin are present (Bingley et al., 1999; Verge et al., 1996). Additionally, taken in aggregate, the use of the level of autoantibody can provide additional predictive information for the persistence of autoantibodies and development of T1D (Barker et al., 2004). Moreover, among metabolic risk markers, the loss of first phase insulin response to intravenous glucose has the same prediction value with multiple positive antibodies when it is associated with one of these autoantibodies (Krischer et al., 2003). Furthermore, the predictive value of having multiple autoantibodies can increase significantly by the presence of a high-risk genotype, with a positive predictive value of 67% in multiple antibody–positive DR3/4 individuals, versus 20% in those without DR3/4 (Yamamoto et al., 1998). While, high sensitivity and specificity are required for detection of prediabetes in the general population where the prevalence is of the order of 0.3% even when genetic susceptibility markers are also included (Hermann et al., 2004).

2.1.1 Islet cell autoantibodies

These are markers with best predictive value (Bonifacio & Christie, 1997), because of their high sensitivity to the pancreatic insulite (Kulmala et al., 1998) and their high specificity for T1D (Gorsuch et al., 1981).

Islet cell autoantibodies (ICAs) have been the first disease-specific autoantibodies to be described in patients with T1D (Bottazzo et al., 1974). They appear until ten years before the clinical onset of diabetes (Riley et al., 1990). ICA corresponds to a compounding of different specificities antibodies, because they can be fixed on all cellular types of antigenic structures present in the islet cell cytoplasm (Atkinson & Maclaren, 1993).

High ICA levels could be a marker of strong autoimmune reaction and accelerated depletion of beta-cell function (Zamaklar et al., 2002). In prediabetic subjects, a higher ICA titer is associated with a higher risk for T1D development (Mire-Sluis et al., 2000). In newly diagnosed type 1 diabetic patients, ICAs are present in 80%, and ICA reactivity often waned after diagnosis, with no more than 5% to 10% of patients remaining ICA positive after 10

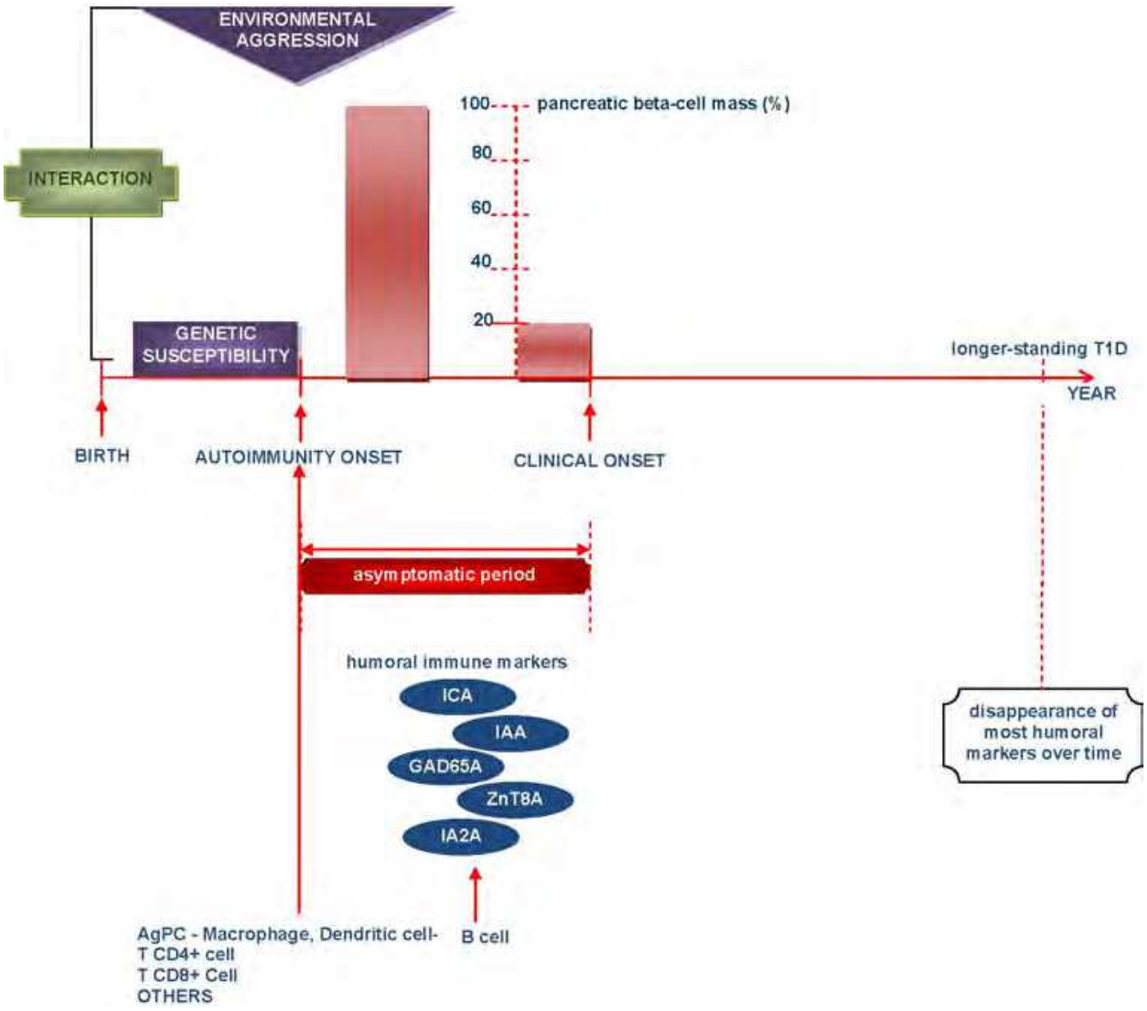

Fig. 1. Natural history of type 1 diabetes. *AgPC: antigen-presenting cell; GAD65A: glutamic acid decarboxylase 65 autoantibody; IAA: insulin autoantibody; ICA: islet cell autoantibody; ZnT8A: zinc transporter 8 autoantibody.*

years (Gilliam et al., 2004). The frequency of the positive ICA is 80% to 100% (Schatz et al., 1994) of revelation for a 25 years old T1D or less (Elfving et al., 2003). It decreases remotely by the primo-decompensation, reaching approximately 3% in related subjects aged of less than 20 years (Schatz et al., 1994).

ICAs are highlighted by indirect immunofluorescence (Borg et al., 2002a; Elfving et al., 2003; Perez-Bravo et al., 2001) on sera incubated with human blood group O pancreas (Takahashi et al., 1995; Thivolet & Carel, 1996). They can be also detected by complementary-fixing antibody (Knip et al., 1994; Montana et al., 1991), since they mainly belong to the IgG1 subclass antibodies (Bottazzo et al., 1980). The increase in ICAs may indicate the presence of other autoantibodies, corresponding to more IgG1subclasses (Dozio et al., 1994). Association with other autoantibodies increases the test specificity, with a decrease in sensitivity however (Thivolet & Carel, 1996). ICA levels that exceed 80 JDF (Juvenile Diabetes Foundation) units at the time of diagnosis despite better beta-cell function are associated with short clinical remission (Zamaklar et al., 2002), and include 53% of disease

development risk in five years following their revelation (Dozio et al., 1994). Nevertheless, the high levels of ICA found in the family relatives do not necessarily lead to T1D development (Bingley, 1996). Likewise, the low rates of these antibodies lessen the disease risk (Bonifacio et al., 1990).

2.1.2 Insulin autoantibodies

It would be important to recall that protective alleles of insulin gene *INS VNTR* (variable number of tandem repeats) are associated with higher levels of *INS* messenger RNA expression in the thymus (Aribi, 2008; Pugliese et al., 1997; Vafiadis et al., 1997). Insulin would then be the main antigens engaged in thymic T cell education and immune tolerance induction. Therefore, it has been the first diabetes-related autoantigen to be identified (Gilliam et al., 2004).

Insulin autoantibodies (IAAs) are of weak prevalence at the time of diagnosis (Breidert et al., 1998). Their levels are increased especially in prediabetics (Palmer et al., 1983), but also in newly diagnosed type 1 diabetic subjects. Additionally, IAAs could be confused with insulin antibodies (IAs) produced following injection of exogenous insulin; therefore, we cannot assess the real level of IAAs in treated patients (Gilliam et al., 2004).

On the other hand, various studies have shown that the elevated IAA frequency and levels are observed mainly in young children (Landin-Olsson et al., 1992) and HLA DR4 subjects (Achenbach et al., 2004; Savola et al., 1998; Ziegler et al., 1991). Moreover, IAAs could be detected in all children who develop diabetes when they are associated with multiple autoantibodies. Furthermore, these antibodies confer high risk in T1D relatives (Ziegler et al., 1989), essentially in combination with other autoimmune markers (Bingley et al. 1999; Thivolet et al., 2002; Winnock et al., 2001). However, the actual frequency of positivity varies considerably from one study to another, according to the IAA assay, age at diagnosis, as well as the populations studied (Gilliam et al., 2004).

Interestingly, IAAs do not necessarily reflect beta-cell destruction. Indeed, they have been reported to occur in other autoimmune diseases, such as Hashimoto thyroiditis, Addison disease, chronic hepatitis, pernicious anemia, systemic lupus erythematosis, and rheumatoid arthritis (Di Mario et al., 1990).

IAAs can be detected by two assay methods, a fluid-phase radioimmunoassay (RIA) and a solid-phase enzyme-linked immunosorbent assay (ELISA); however, it has been shown that IAAs measured by RIA were more closely linked to T1D development than those measured by ELISA (Murayama et al., 2006; Schlosser et al., 2004; Schneider et al., 1976; Wilkin et al., 1988).

2.1.3 Glutamic acid decarboxylase autoantibodies

Of note, a 64kDa islet cell protein was initially isolated by precipitation with autoantibodies present in sera of patients with T1D (Baekkeskov et al., 1982). After laborious searches, this protein was identified as glutamic acid decarboxylase (GAD) (Baekkeskov et al., 1990); the enzyme that synthesizes the gamma-aminobutyric acid neurotransmitter in neurons and pancreatic beta-cells (Dirkx et al., 1995). At that time, GAD autoantibodies had been demonstrated to have a common identity in patients with stiff-man syndrome (SMS) and T1D (Baekkeskov et al., 1990; Solimena et al., 1988). During the same period, GAD complementary deoxyribonucleic acid (GAD cDNA) cloning demonstrate that there are two different genes of GAD, designated GAD1 and GAD2 (Bu et al., 1992; Erlander et al., 1991; Karlsen et al., 1991),

located on chromosome 2q31.1 and chromosome 10p11.23, respectively (Bennett et al., 2005). GAD1 mRNA has been reported to be translated into GAD67, which is not detected in human islets (Karlsen et al., 1991), but is predominantly found in mouse islets (Petersen et al., 1993; Velloso et al., 1994). The mRNA for GAD2 gene encodes the GAD65kDa isoform that is expressed in human pancreatic islets and brain (Gilliam et al., 2004).

GAD65 autoantibodies (GAD65A) are revealed in 70% to 80% of cases among prediabetic subjects and newly diagnosed patients (Kulmala et al., 1998). They are considered as a good retrospective marker of the autoimmune progression, because of their persistence in the sera of patients with T1D for many years following diagnosis (Borg et al., 2002b). Whereas, these antibodies have a low positive predictive value for beta-cell failure (47%) compared to ICAs (74%) (Borg et al., 2001) and can be revealed in patients with neurological disorders, including those with gamma-aminobutyric acid (GABA)-ergic alterations (Piquer et al., 2005; Solimena et al., 1990). Similarly, they can be present in patients who have other autoimmune diseases (Davenport et al., 1998; Nemni et al., 1994; Tree et al., 2000) as well as in patients with type 2 diabetes (Hagopian et al., 1993; Tuomi et al., 1993). Consequently, they don't seem to be specific to pancreatic beta-cells destruction (Wie et al., 2004; Costa et al., 2002).

GADAs are usually detected by radioligand-binding assay, which is reported to have higher sensitivity, specificity, and reproducibility than other methods using ELISA, enzymatic immunoprecipitation, and immunofluorescence assays (Damanhouri et al., 2005; Knowles et al., 2002; Kobayashi et al., 2003).

2.1.4 Anti-tyrosin phosphatase autoantibodies

These antibodies are directed against two digestion fragments (Jun & Yoon, 1994; Maugendre et al., 1997) resulting from trypsin hydrolysis of transmembrane protein expressed in islets and the brain, and are present in two related forms with distinct molecular weights, 40kDa and 37kDa (Bonifacio et al., 1995a; Li et al., 1997; Yamada et al., 1997).

Of note, the 40kDa antigen is the receptor tyrosine phosphatase-like protein IA-2 associated with the insulin secretory granules of pancreatic beta-cells (Trajkovski et al., 2004), also called islet cell autoantigen 512 (ICA512)/IA-2 (Bonifacio et al., 1995b; Payton et al., 1995). The 37kDa antigen is a tryptic fragment related protein tyrosine phosphatase, designated IA-2β/phogrin (Kawasaki & Eisenbarth, 2002), or islet cell autoantigen-related protein tyrosine phosphatase (IAR) (Lu et al., 1996).

It has been shown that antibodies to the two antigens have similar sensitivity; however, epitope mapping studies have suggested that antibodies to IA-2 (IA-2A, insulinoma-associated protein 2 islet tyrosine phosphatase) appear to be more important for the pathogenesis of T1D than those to IA-2β (Savola, 2000; Schmidli et al., 1998). In fact, the binding of phogrin autoantibodies could be totally blocked if adding ICA512 to sera positive for both ICA512 and phogrin, while the binding of ICA512 antibodies cannot be fully blocked with phogrin (Savola, 2000).

IA-2As can be evaluated by radioligand-binding assay and ELISA (Bonifacio et al., 2001; Chen et al., 2005a; Kotani et al., 2002); whereas, RIAs performed much better than ELISAs, as was found for GAD65A assays (Verge et al., 1998).

2.1.5 Zinc transporter 8 autoantibodies

The human beta-cell-specific zinc transporter Slc30A8 (ZnT8) is a member of the large cation efflux family of which at least seven are expressed in islets (Chimienti et al., 2004). It has

been recently defined as a major target of humoral autoimmunity in human T1D based on a bioinformatics analysis (Dang et al., 2011; Wenzlau et al., 2009). Autoantibodies to ZnT8 (ZnT8A) have been therefore detected in high prevalence in newly diagnosed type 1 diabetic patients (Yang et al., 2010) and obviously overlap with GADA, IA2A, and IAA (Wenzlau et al., 2007).
Of note, ZnT8 autoimmunity could be an independent marker of T1D, given that ZnT8As can be present in antibody-negative individuals and in type 2 diabetes, and in patients with other autoimmune disorders (Wenzlau et al., 2008).
Antibodies to ZnT8 can be measured by radioimmunoprecipitation assay using 35^S labelled methionine *in vitro* translation products of different fragments of human ZnT8 (Lampasona et al., 2010).

2.2 Immunological anomalies of type 1 diabetes and cellular autoimmunity

In reality, our understanding of the exact cellular immune mechanisms that lead to the development of T1D is limited, and it is possible that the potential target autoantigens may be less well defined and more diverse, probably because of the epitopes diversification.
The immune reaction against beta-cells is due primarily to a deficit in the establishment of central thymic tolerance and the activation of potentially dangerous autoreactive T cells and B cells that recognize islet antigens. Additionally, aggression of the beta-cells may be initiated by other cells and components of the innate immune system. In fact, it has been observed that the immune cells peripheral infiltration of the Langerhans islets, a process termed perished-insulitis, begins initially with the monocytes/macrophages and dendritic cells (DCs) (Rothe et al., 2001; Yoon et al., 2005; Yoon et al., 2001). Upon exposure to antigens, islet-resident antigen presenting cells, likely DCs, undergo maturation, leading to the expression of cell surface markers that are subsequently required for T cell activation in the pancreatic lymph nodes (panLN). CD4+ T cells and macrophages home to islets and release pro-inflammatory cytokines and other death signals that acutely trigger necrotic and pro-apoptotic pathways (Fig. 2).

2.2.1 T cells and B cells

Although both humoral and cell-mediated immune mechanisms are active during T1D, CD4+ and CD8+ T cells recognizing islet autoantigens are the main actors of beta-cells death (DiLorenzo et al., 2007; Gianani & Eisenbarth, 2005; Toma et al., 2005). B cells may play a role in inducing inflammation and presentation of self-antigen to diabetogenic CD4+ T cells (Silveira et al., 2007).
It has been repeatedly observed that the pancreatic islets of diabetic patients prior to and at diagnosis are infiltrated by T lymphocytes of both CD4 and CD8 subsets (Hanninen et al., 1992; Imagawa et al., 2001; Kent et al., 2005). Additionally, their circulating number among type 1 diabetic patients is higher than those of B cells (Martin et al., 2001). Moreover, the disease can be transferred to NOD-*scid* mice that are genetically deficient in lymphocytes (Christianson et al., 1993; Sainio-Pollanen et al., 1999; Yamada et al., 2003), or to newborn NOD mice exposed to atomic radiation (Miller et al., 1988; Yagui et al., 1992) by injection of T CD4+ and CD8+ spleenocytes from prediabetics. However, injection of anti-islets antibodies does not induce autoimmunity (Timist, 1996) and beta-cell damage may develop in individuals with severe B cells deficiency (Martin et al., 2001).

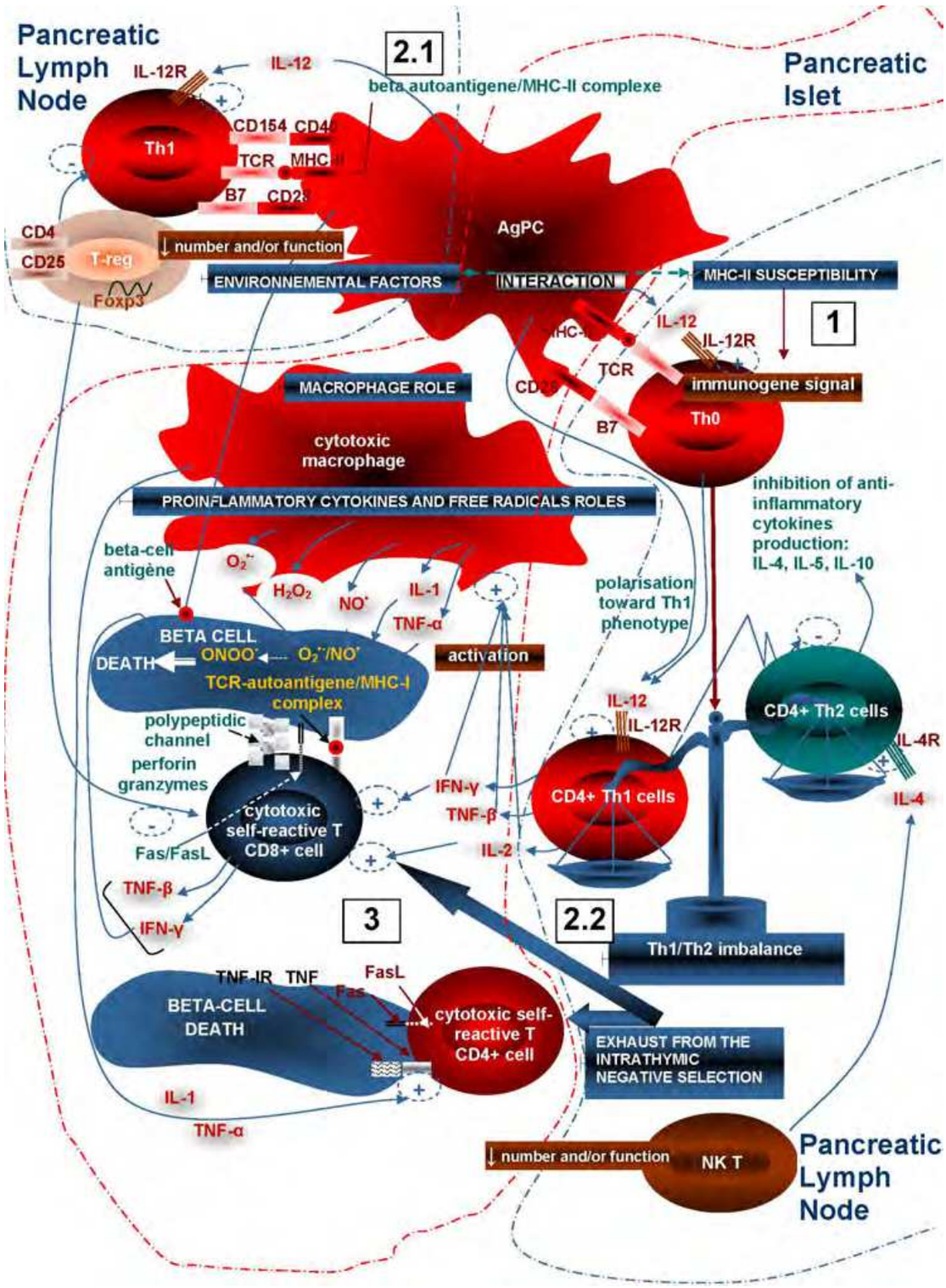

Fig. 2. Hypothetical scheme of the autoimmune response of type 1 diabetes: cellular interaction and molecules that can be involved within the destruction of pancreatic islets beta-cells. *(1) Antigen exposure and TCR signalling pathway: AgPC exposes epithopes derived from*

beta-cells on its membrane surface by some class II MHC molecules that are involved in the susceptibility of T1D. The autoantigens/class II MHC complex, adhesion molecules, particularly B7, IL-12 derived from AgPC, and possibly other immunogenic signals, could join and cause the activation of CD4+ Th0 cells. Many factors (physical, psychological, and chemical stress) are able to guide the Th0 differentiation towards Th1 cell. (2.1 and 2.2) Activation of Th1 cells: immunogenic signals resulting from class II MHC/peptide-TCR, CD40-CD154 and CD28-B7 interactions induce the activation of Th1 cells. (3) Beta-cells destruction: activated Th1 cells produce IL-2, TNF-β and IFN-γ cytokines, increasing the activation of islet-infiltrated macrophage and autoreactive cytotoxic CD8+ cells. These cells can destroy pancreatic beta cells by proinflammatory cytokines, granzymes and perforin, FasL-Fas interaction, and oxygen/nitrogen free radicals. Anomalies of autoreactive T cells suppression could be due to the decreased number and/or function of peripheral regulatory cells affecting both NK T cells and natural CD4+CD25+/CD25highFoxp3+ T-reg cells. AgPC: antigen-presenting cell, CD: cluster of differentiation, DC: dendritic cell, Fas/FasL: CD95/CD95 Ligand, Foxp3: transcription factor forkhead box P3, IFN: interferon, IL: interleukin, MHC: major histocompatibility complex, NK T: natural killer T cell, T1D: type 1 diabetes, TCR: T cell receptor, Th: T helper, TNF: tumor necrosis factor.TNF-RI: tumor necrosis factor receptor type I.

2.2.2 CD4+ and CD8+ T cells and ways of beta-cells destruction

The precise role of each of these cells in pancreatic islets destruction remains unclear and controversial. Therefore, two main pathways may be involved in triggering the disease, both of which are activated following recognition of beta-cell autoantigens.

According to the indirect way, the critical role in T1D development could be attributed to autoreactive CD4 T cells, as exemplified by the observation that the major histocompatibility complex class II (MHC II) genes are the main candidate genes to which a key role can be assigned in the autoimmune process according to their strong association with the disease (Aribi, 2008; Concannon et al., 2009). These cells can initiate beta-cells destruction and lead to tissue cell damage (Peterson & Haskins, 1996), through the secretion of cytokines with toxic effects (Amrani et al., 2000), then recruit T CD8+ lymphocytes (McGregor et al., 2004).

According to the direct way, autoreactive T CD8+ lymphocytes (Anderson et al., 1999) could initiate beta-cells destruction, as shown in transgenic TCR (NOD/AI4αβ Tg) NOD mice, that T1D autoimmunity beginning can be achieved in total absence of CD4+ T cells and requires only CD8+ T cells (Graser et al., 2000). Additionally, disease development is reduced only when adult NOD mice are injected with anti-class I MHC molecules or anti-CD8 mAb molecules (Wang et al., 1996). Moreover, β2-microglobulin-deficient ($\beta 2m^{-/-}$) and anti-CD8 mAb-treated NOD mice, yet deficient in CD8+ T cells develop neither insulitis nor T1D (Yang et al., 2004).

However, direct evidence for these observations is compelling only in animal models in which adoptive transfer experiments are feasible ethically (Di Lorenzo et al., 2007). Additionally, several differences can be revealed between men and animal models of T1D. For example, in men, immunohistological studies of type 1 diabetic pancreatic-biopsy showed a strong number of islet-infiltrated CD8+ cytotoxic T cells compared to that of islet-infiltrated CD4+ T helper cells (Itoh et al., 1993). In contrast, in NOD mice, pancreatic islets are infiltrated predominantly by CD4 + T cells compared to CD8+ T cells (Kida et al., 1998).

2.2.3 Regulatory T cells/effectors T cells imbalance

The primary function of Treg cells is the maintenance of self-tolerance in order to prevent the development of autoimmune diseases (Sakaguchi et al., 1995). They also have the ability

to control a runaway immune response by different feedback mechanisms, involving the production of anti-inflammatory cytokines, direct cell-cell contact or modulating the activation state of antigen-presenting cells (AgPCs) (Corvaisier-Chiron & Beauvillaina, 2010). Normal tolerance to self-antigens is an active process that has a central component and a peripheral component. Central tolerance implies induction of tolerance in developing lymphocyte when they encounter self-antigens that are present in high concentration in the thymus or bone marrow; while peripheral tolerance is maintained by mechanisms of self-reactive T cells elimination by clonal deletion, anergy or ignorance (Wallace et al., 2007). Among these three mechanisms only the deletion is induced by Treg cells (Corvaisier-Chiron & Beauvillaina, 2010).

Different subpopulations of Treg cells have been identified: natural Treg (nTreg) cells that drived from the thymus and migrate to peripheral tissues, and peripherally induced Treg (iTreg) (Corvaisier-Chiron & Beauvillaina, 2010). nTreg cells represent 2-4% of circulating lymphocytes in humans (Wahlberg et al., 2005) and are characterized by the expression of CD4, $CD25^{high}$, $CD127^{low}$ molecules and high levels of the transcription factor FoxP3 (forkhead box P3) (Corvaisier-Chiron & Beauvillaina, 2010; Wahlberg et al., 2005). They also express surface CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) and GITR (TNF receptor family glucocorticoidinduced-related gene) involved in membrane mechanisms of Treg suppression (Corvaisier-Chiron & Beauvillaina, 2010).

Except pathological conditions, there is a balance between regulatory T cells and effector T cells. Some genetic and environmental factors might cause deregulation of this balance in favor of self-reactive lymphocytes that may induce or predispose to the development of autoimmune diseases, including T1D (Brusko et al., 2008).

In NOD mice and diabetic patients and in several organ-specific animal models of autoimmunity as well as in humans (Furtado et al., 2001; Kriegel et al., 2004; Kukreja et al., 2002), it has been demonstrated that number and/or function of peripheral regulatory cells affecting both nTreg cells (CD4+CD25+Foxp3+) (Fontenot et al., 2003; Hori et al., 2003; Khattri al., 2003) and natural killer (NK) T cells (Duarte et al., 2004; Hong et al., 2001) are decreased; while self-reactive peripheral T cells number is increased (Berzins et al., 2003). Additionally, decreased contacts between effectors and nT-reg cells seem to belong to additional events leading to autoreactive T cells activation and proliferation (Lindley et al., 2005; Maloy & Powrie, 2001; Piccirillo et al., 2005).

On the other hand, various studies showed that T1D in both humans and NOD mice could be due to the weak secretion of IL-4 resulting from a deficiency in NK T cells (Lehuen et al., 1998; Wilson et al., 1999) and that diabetes can be prevented in mice by transfer of NK T cell–enriched $CD4^-CD8^-$ double negative cells (Baxter et al., 1997; Falcone et al., 1999; Lehuen et al., 1998) or of thymic-derived nT-reg cells (Chen et al., 2005b; Lindley et al., 2005; Luo et al., 2007).

2.2.4 Regulatory T cells/Th17 cells imbalance

Th17 cells represent a subtype of T cells that can be generated in the presence of IL-23 even from cells deficient in transcription factors required for Th1 (T-bet) or Th2 (GATA-3) cells development (Harrington et al., 2005; Park et al., 2005). However, IL-23 would not be a factor for Th17 cells differentiation but rather intervene in their survival and proliferation. In fact, naive T cells do not express receptors for IL-23 and do not differentiate into Th17 cells only in the presence of IL-23 (Mangan et al., 2006). Additionally, Th17 cells express a specific

transcription factor, RORC2 (retinoic acid receptor-related orphan receptor C2, known as RORγt in mice), which is crucial for the generation of Th17 cells, especially *via* the transcriptional induction of the gene encoding IL-17 and the expression of IL-23 receptor (Ivanov et al., 2006). To acquire a full differentiation of such cells, RORC2 acts in cooperation with other transcription factors, including RORα, STAT3, IRF-4 and Runx1 (Miossec et al., 2009).

The discovery of factors involved in the differentiation of Th17 and Treg cells suggests the existence of Treg/Th17 balance, controlled by IL-6 (Kimura et al., 2011). More recently, increased Th17 immune responses or imbalance of nTreg cells and IL-17 producing Th17 have been found to be associated to the onset of the disease in both humans and NOD mice or Diabetes-prone BioBreeding (DP-BB) rats (Honkanen et al., 2010; Shi et al., 2009; van den Brandt et al., 2010). While, these observations should be confirmed further.

2.2.5 Th1/Th2 imbalance

Different factors, including physical, psychological, and chemical stress (Ernerudh et al., 2004) can produce imbalance in the proportions of CD4+ Th1 cell and CD4+ Th2 cell subsets (Eizirik et al., 2001; Rabinovitch et al., 1994; Thorvaldson et al., 2005). Several studies have shown that the autoimmune aggression leading to T1D involves Th1 cells (Kida et al., 1999; Sharif et al., 2002; Yoon & Jun, 2005). However, Th2 cells seem to be associated with protection against beta-cells destruction (Cameron et al., 1997; Ko et al., 2001; Suarez-Pinzon & Rabinovitch, 2001).

In NOD mouse model, T1D can be transferred among animals through the injection of Th1 cells (Kukreja et al., 2002). T1D-sex relationship has been linked to the type of produced cytokines. Lymphocytes infiltrating female mice pancreatic islets produce high levels of Th1 cytokine mRNA and low levels of Th2 cytokine mRNA. On the other hand, male mice are more resistant to T1D because they produce more Th2 cytokine mRNA and less cytokine Th1 mRNA (Azar et al., 1999; Fox & Danska, 1997). Likewise, young NOD mice spleenocytes expressing CD62L and CD25, *i.e.* CD4+CD45RB^{low} (memory/activated cells) which are involved in dominant protection against T1D development, show an overproduction of Th2 cytokines, yet tend towards an overproduction of Th1 cytokines right before diabetes onset (Shimada et al., 1996). Besides, female NOD mice have more spleenocytes CD45RB^{low} CD4+ and more spleenocytes CD4+CD25+ activated helper cells than do male NOD mice have (Azar et al., 1999). Moreover, it is possible to prevent T1D in NOD mice with a single injection of insulin or GAD peptide (Han et al., 2005), because it causes a reduction in levels of Th1 cytokines and an increase in the ones of Th2 cytokines (Muir et al., 1995; Sai et al., 1996).

2.2.6 Innate immunity

It has been recently observed that innate immunity may play a critical role in the development of T1D. This observation has been supported by works showing that infusions of alpha-1 antitrypsin, a serine protease inhibitor that protects tissues from enzymes produced from inflammatory cells, were found to reverse new-onset diabetes in NOD mice (Koulmanda et al., 2008). Many effects have been described, including reduced insulitis, enhanced beta-cell regeneration, and improvement in peripheral insulin sensitivity (Luo et al., 2010).

Thanks to many experiments conducted in animal models, it has been shown that toll-like receptors (TLRs), as part of the innate immune system, may have an important role in T1D

development (Filippi & von Herrath, 2010). For example, injection of low dose of TLR-3 stimulus poly I:C has been shown to prevent diabetes in the disease-prone Biobreeding rat model (Sobel et al., 1998). In addition, TLR deficiency has been associated with decreased number of some Treg. Indeed, T cells with a regulatory phenotype can express TLR-2, TLR-4, TLR-5, TLR-7 and TLR-8 (Caramalho et al., 2003; Sutmuller et al., 2006), and the proliferation of Treg cells has been observed especially following the administration of TLR-2 ligands to TLR-2-deficient mice (Sutmuller et al., 2006). Moreover, it has been suggested that protection against T1D in NOD mice through infection with Lymphocytic Choriomeningitis Virus (LCMV) is dependent on the emergence of Tregs and TLR-2 (Boettler & von Herrath, 2011).

2.2.7 Macrophages

Macrophages play a significant role in the oxidative stress (Ishii et al., 1999; Rozenberg et al., 2003), innate immunity (Bedoui et al., 2005; Lawrence et al., 2005) and inflammation (Ishii et al., 1999; Lawrence et al., 2005). Macrophages and other AgPCs in the panLN (Pearl-Yafe et al., 2007) initiate T cell sensitization, and concomitantly activate regulatory mechanisms (Kaminitz et al., 2007). The central role of macrophages in the cellular immune response (Durum et al., 1985) and in the development and activation of beta-cell-cytotoxic T cells during T1D (Yoon & Jun, 2001) has been previously proven in BioBreeding (BB) rats where a macrophage insulitis preceding lymphocyte insulitis could be prevented by a silica intraperitoneal injection (Albina et al., 1991). However, macrophages are also able to exert a suppressor effect on lymphocyte proliferation (Albina et al., 1991; Taylor et al., 1998; Zhang & McMurray, 1998). This effect is exerted on T and B cells alike and is mediated by several ways involving especially prostaglandins and nitric oxide as metabolic mediators (Albina et al., 1991; Ding et al., 1988; Jiang et al., 1992).

A mechanism by which macrophages intervene preferentially in Th1 and Th2 clones differentiation has been suggested. Hence, macrophages can interact with Th cells and induce polarization toward the Th1 or Th2 cell subset depending on the oxidation level of their glutathione content. With low levels of oxidized glutathione, they induce a polarization toward Th1 phenotype, whereas high levels of oxidized glutathione lead to Th2 differentiation (Murata et al., 2002). Additionally, some IL-12 antigenic stimulations induce Th1 cells activation (Hsieh et al., 1993). Th2 cells activation goes through the action of IL-4 and IL-10, which can also be produced by activated macrophages in the presence of immune complexes (Fiorentino et al., 1991).

2.2.8 Dendritic cells

DCs play an important role in initiating the immune response and antigen presentation, as well as in maintaining peripheral self-tolerance (Steinman et al., 2003). There are mostly immature DCs (iDCs), which have poor antigen presentation functions (de Vries et al., 2003), may be involved in immunoregulatory functions in autoimmune processes (Dorman et al., 1997). These functions depend largely on co-stimulation during the maturation process. Thus, tolerogenic DCs are iDCs with reduced allostimulatory capacities and low expression levels of costimulatory molecules, like CD40, CD80 and CD86 molecules. However, the transition to the mature state, following exposure to pathogens, leads to increased antigen presentation and expression of T cell co-stimulatory molecules and T cell responses (Steinman & Banchereau, 2007).

Nevertheless, the acquisition of a high degree of maturity and expression of adhesion molecules, especially CD86 molecule, allows the DCs to provoke the activation of $CD4^+CD25^+$ regulatory T cells capable of inhibiting autoimmune disease (Yamazaki et al., 2003). It is therefore quite possible that the DCs involved in triggering the autoimmune process leading to T1D (Clare-Salzler et al., 1992; Feutren et al., 1986; Mathis et al., 2001), are mature cells with a large capacity for antigen presentation, but without effect on regulatory T cells.

Additionally, it has been shown that DCs are the initiators of the islet infiltration in NOD mice (DiLorenzo et al., 2007). Such cells isolated from the panLN could prevent diabetes development when transferred adoptively to young recipients (Bekris et al., 2005), while those from other sites could not, suggesting that the activation of autoreactive T cells occurs at this site and that their suppression would be due to deletion or regulation mechanisms (Belz et al., 2002; Hugues et al., 2002).

2.2.9 Adhesion and costimulation molecules and cell signaling

T-cell-receptor (TCR)-mediated recognition of pancreatic autoantigens is a central step in the diabetes pathogenesis (Bach, 2002). Interaction between TCR and pancreatic peptides aberrantly complexed with class II MHC molecules on pancreatic beta-cells (Foulis, 1996) or expressed on the AgPCs in panLN is required for the activation of Th1 lymphocytes. Similarly, TCR interaction with autoantigen peptides presented by class I MHC molecules on pancreatic beta-cells is essential for the activation of cytotoxic CD8+ autoreactive T lymphocytes in pancreatic islet. Activated Th1 cells induce positive signals involving IL-2, TNF-β and IFN-γ cytokines to increase the activation of islet-infiltrated macrophage and cytotoxic CD8+ cells.

Beta-cells aggression can be mediated by proinflammatory cytokine-mediated cell killing (IL-1 (Aribi et al., 2007; Sparre et al., 2005), TNF-α (Christen et al., 2001; Lee et al., 2005), TNF-β, IFN-γ, IL-18 (Nakanishi et al., 2001; Szeszko et al., 2006), IL-12 (Giulietti et al., 2004; Holtz et al., 2001), IL-6 (Kristiansen & Mandrup-Poulsen, 2005; Targher et al., 2001), and IL-8 (Erbağci et al., 2001; Lo et al., 2004), etc.), granzymes (GRZ) and perforin (PRF1), FasL-Fas (CD95L-CD95) interactions, hydrogen peroxide and free radicals (Mukherjee & DiLorenzo, 2010).

Numerous adhesion molecules and signalling proteins, can amplify activation of the CD3/TCR complex leading to self-reactive T cells proliferation within panLN. Experimental NOD mice studies highlighted three principal costimulation pathways for such activation: CD28-B7, CD40-CD40L (CD 154) (Bour-Jordan et al., 2004) and NKG2D-RAE-1 (von Boehmer, 2004). Therefore, it has been previously shown that the T1D occurrence is decreased by injection of anti-B7.2 mAb's (Lenschow et al., 1995). Meanwhile, invalidation of B7.2 (CD86) (NOD/B7.2$^{-/-}$) confers protection against the disease (Salomon et al., 2001). Additionally, ablation of CD40-CD40L pathway with neutralizing antibodies (anti-CD40L mAb's) or with invalidation of CD40L (NOD/B7.2$^{-/-}$) prevents the early stages of T cell activation in the panLN (Green et al., 2000). Moreover, it has been demonstrated that the activated islet-infiltrated CD8+ T cells express NKG2D molecules and that the treatment of NOD mice with anti-NKG2D mAb's can prevent T1D development (Ogasawara et al., 2004).

2.2.10 Vitamin D status

The gradual increase in the frequency of T1D from the Equator to the Poles, especially among children born in spring or early summer and in the winter months has been

interpreted as the consequence of limited exposure to sun and low vitamin D status. Additionally, case-control studies have consistently demonstrated an association between the incidence of T1D and vitamin D status in children and pregnant women, and an inverse relationship between vitamin D intake from diet and supplements and seasonal variations in the incidence of T1D (Pittas & Dawson-Hughes, 2010).

Experimental data could also confront the observation about the relationship between vitamin D and T1D. Indeed, the insulin-producing beta-cells, as well as other cell types of the immune system (Stoffels et al., 2006), express the vitamin D receptor (VDR) and 1-alpha-hydroxylase enzyme (Nikalji & Bargman, 2011). By regulating the extracellular calcium concentration and transmembrane calcium fluxes, vitamin D may extend to preservation of insulin secretion and insulin sensitivity. Besides, vitamin D has immunomodulatory properties and is able to affect the autoimmune process leading to T1D (Bobryshev, 2010).

3. Immunotherapy of type 1 diabetes

Intervention and prevention strategies currently under consideration for T1D aim to reverse immune autoreactivity and restore beta-cell mass (Boettler & von Herrath, 2010; Bougneres et al., 1988). Immunotherapy can be used to induce immunological tolerance to beta-cell antigens using various protocols (Haase et al., 2010), involving both islets antigen-non-specific and antigen-specific approaches, but so far success has been limited.

Immunomodulation strategies have been generally achieved in two stages of the disease: prior to clinical onset but after the appearance of islet autoantibodies (secondary prevention) and immediately after diagnosis (intervention) (Staeva-Vieira et al., 2007) (Fig. 3). Based on the preclinical and clinical outcomes of studies using these therapies, combination with islet

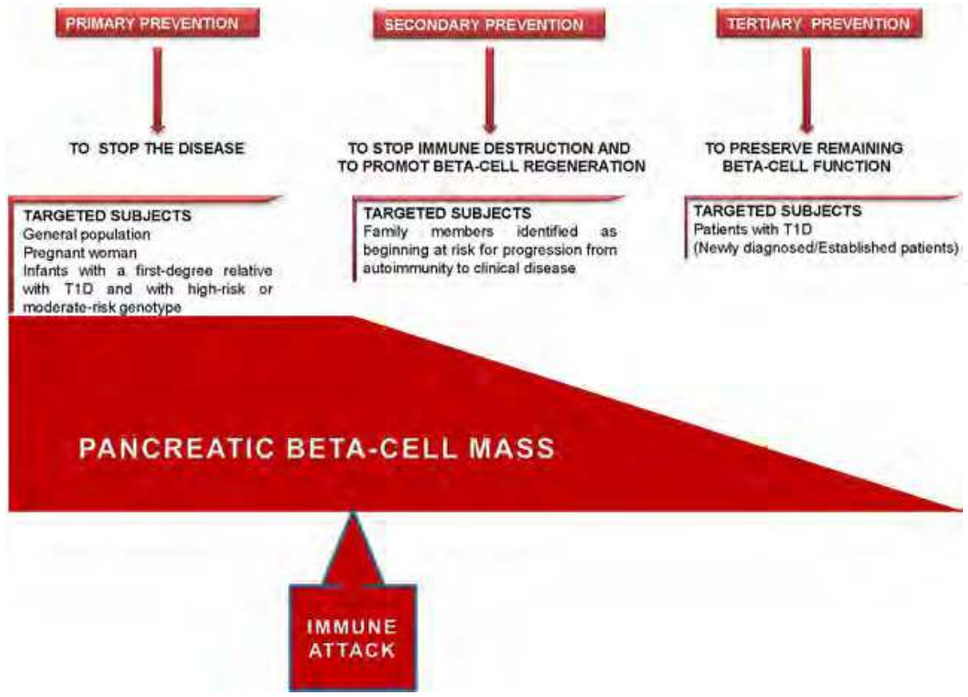

Fig. 3. Stages of type 1 diabetes prevention: objectives and selective targeting.

transplantation or stem cells for beta-cell regeneration are required in order to re-establish peripheral tolerance and to achieve a lasting remission (Marin-Gallen et al., 2010). Nevertheless, it is important to select eligible patients for such therapy, both to avoid toxicity and improve the chances of successful treatment (June & Blazar, 2006).

3.1 Non-antigen-specific immunotherapeutic approach for type 1 diabetes

For non-antigen-specific immunomodulation approch, many protocols using chemical- and antibody-mediated therapies have shown promise to the effects of various immunosuppressive drugs, including cyclosporine A (CsA), corticoïdes, azathioprine, T cell modulators (anti-CD3, anti-thymocyte globulin (ATG)), B cell-depleting agents (Rituximab**:** anti-CD20), anti-inflammatory molecules (anti-interleukin (IL)-1, anti-tumour necrosis factor (TNF)-α and anti-TNF-γ), cytokine-receptor-directed therapies and small-molecule protease inhibitors (Boettler & von Herrath, 2011; Luo et al., 2010; Sia, 2005; Silverstein et al., 1988) (Table 1). However, we have to acknowledge that these drugs increase the risk of developing infections and malignancies, favor the occurrence of metabolic complications such as dyslipidemia and hypertension and that some of them have been shown to inhibit beta-cell regeneration (Nir et al., 2007; Vantyghem et al., 2009). In addition to the immunosuppressant toxicity, recurrence or persistence of the autoimmune process has been observed after withdrawal of the immunosuppressive agents.

Immunomodulation therapies with nicotinamide and Bacillus Calmette-Guérin (BCG) have been tested in many clinical T1D prevention trials, but they showed no advantageous effects (Huppmann et al., 2005). Despite these negative results, large placebo-controlled clinical trials continue to illustrate the efficacy of these drugs in preventing T1D in newly diagnosed patients or in first-degree relatives of subjects with the disease.

Other immunomodulatory drugs that directly target immune cells have also been tested with success, especially in animal models of T1D, but some of them have run into major difficulties. They include DCs-based therapy, mainly the endocytic receptor involved in antigen processing and presentation DCs (DEC-205 (Ly75/CD205)), drugs targeting T cells (CTLA4-Ig: anti-CD4, anti-CD45) (Staeva-Vieira et al., 2007; Gregori et al., 2005), AgPCs (antibodies to CD40L or CD40) and NK T cells (alpha-galactosyl-ceramide (α-Gal-Cer), etc. (Chen et al., 2005c; Hong et al., 2001; Rewers & Gottlieb, 2009).

Although most of the immunomodulator treatments induce Treg cells activation, the direct infusion of ex vivo-expanded regulatory T cells has been considered to be a potential to prevent T1D (Lundsgaard et al., 2005; Tang et al., 2004; Tarbell et al., 2004) as well as other diseases, such as systemic lupus erythematosus (SLE) (Zheng et al., 2004), multiple sclerosis (MS) (Kohm et al., 2002) and inflammatory bowel disease (IBD) (Mottet et al., 2003). Treg-based cell therapy must meet at least four important therapeutic criteria: to (1) avoid the induction of immunogenicity of the infused cells; (2) prevent or delay cellular immunosenescence; (3) maximize help; and (4) be cognizant of the known differences between mouse and human T-cell biology (June & Blazar, 2006).

Moreover**,** drugs targeting adhesion molecules, such as Alefacept (antibody to leucocyte function-associated antigen-3 (LFA-3)), Efalizumab (antibody to LFA-1), FTY720 (immunosuppressive drug inhibiting activated T cell extravasation and trafficking to sites of inflammation), show promise in a significant proportion of patients with other diseases and are therefore of high potential interest for testing in T1D (Staeva-Vieira et al., 2007).

Therapeutic agent	Methodof delivery	Phase	Population targeted	ClinicalTrials.gov identifier
Otelixizumab	SC	III	ND	NCT00946257 NCT00451321 NCT00678886 NCT01123083
Teplizumab	IV, SC	I/II	ND	NCT01030861 NCT00378508 NCT00870818 NCT00806572
INGAP peptide	SC	II	EP	NCT00995540 NCT00071409
Peptide-MHC class II dimmers	PRT	//	//	*No trials on humans*
CsA	O	PS	ND	*NCT/URL links no longer available*
Nicotinamide	O	ES	SR	*NCT/URL links no longer available*
Atorvastatin	O	I	ND	NCT00974740
BCG	ID	I	ND	NCT00607230
Gluten-free diet	O	OG	NR	NCT01115621 NCT00279318
DHA	O	II	CR	NCT00333554
BP/Hyd. casein	O	II	CR	NCT01055080 NCT00607230
Vitamin D3	O	I	NR	NCT00141986
Diazoxide	O	IV	ND	NCT00131755
hrIFN-α	O	II	ND	NCT00024518
hrIL-1Ra	SC	III	ND	NCT00711503 NCT00645840
Canakinumab	SC	II	ND	NCT00947427
AAT	O	I	ND	NCT01319331
Rituximab	IV	III	ND	NCT00279305
Alemtuzumab	IV	I	ND	NCT00214214
ATG	IV	II	ND	NCT00515099
CTLA4-Ig	IV	II	ND	NCT00505375
Auto UCB	INF	II	EP	NCT00305344
Auto ODN DC	INF	I	EP	NCT00445913
Prochymal	IV	II	ND	NCT00690066

Table 1. Non-antigen-specific tolerance-based clinical trials for type 1 diabetes. *AAT: alpha 1-antitrypsin (Aralast NP); Alemtuzumab: anti-CD52 monoclonal antibody (Campath 1H®); ATG: anti-thymocyte globulin; Auto ODN DC: autologous dendritic cells treated ex vivo with the mixture of the antisense oligodeoxynucleotides; Auto UCB: autologous umbilical cord blood; BCG: Bacillus Calmette-Guérin; BP/Hyd. casein: bovine protein (cow's milk) or hydrolyzed casein formula; Canakinumab: human anti-interleukin-1β monoclonal antibody; CR: children at risk of T1D; CTLA4-Ig: cytotoxic T lymphocyte antigen-4 immunoglobulin (Abatacept); DHA: docosahexaenoic acid (omega-3 fatty acid supplementation diet); EP: established patients; ES: efficacy studies; hrIFN-a: human recombinant interferon-a (Roferon, Roche); hrIL-1Ra: human recombinant interleukin-1 receptor antagonist (Anakinra [Kineret®]); ID: intradermal; INF: infusion; INGAP: islet neogenesis associated protein (15 amino-acid sequence in INGAP peptide, Exsulin); CsA: cyclosporin A; IV: intravenously; ND: newly diagnosed; NR: newborns at risk of T1D; O: oral; OG: ongoing; Otelixizumab: ChAglyCD3 (aglycosylated human anti-CD3 monoclonal antibody, TRX4); Prochymal: mesenchymal stem cells; PRT: parenteral vaccination; PS: pilot studies; Rituximab: anti-CD20 monoclonal antibody; SC: subcutaneously; SR: subjects at risk of T1D; Teplizumab: hOKT3γ 1 (ala-ala) (mutated human anti-CD3 monoclonal antibody).*

3.2 Antigen-specific tolerance strategies for type 1 diabetes

The interest in induction of antigen-specific tolerance to beta-cell antigens for immune prevention of T1D development increased due to the lack of mild non-antigen-specific immunosuppressive agents. This therapeutic approach improves remarkable longevity and long term health in T1D patients and allows most of them to escape the major degenerative complications (Bach, 2003). It can occur as a result of clonal anergy and deletion of antigen-specific autoreactive T cells or induction of regulatory cells and immune deviation (Peakman & Dayan, 2001).

Paradoxically, the induction of tolerance may not be limited to the immune response against the injected antigen, but could be extended to responses against other antigens by a close proximity mechanism involving immunosuppressive cytokines (Bach, 2003). Therefore, the administration of the antigenic epitope specifically recognized by receptors on autoreactive T cells as part of the beta-cells would be more attractive than the whole antigen administration, given the higher levels of its specificity, but also the relatively modest costs of its synthesis (Atassi & Casali, 2008) (Fig. 4).

Different antigen-specific therapeutic approaches have shown efficacy in mouse models of T1D and have been studied most intensively in terms of inducing tolerance in humans (Boettler & von Herrath, 2010). They mainly include administration of immunogenic epitope peptide or whole protein from islet autoantigen, through parenteral, oral and nasal routes. Most of these approaches have been translated into clinic, but none of them have shown convincing promise in recent-onset T1D so far.

The most important clinical trials that have been reported with particular interest have focused on oral administration of parenteral and oral insulin clinical trials, efficacy and safety study on subcutaneous administration of heat-shock protein peptide (hsp60), DiaPep277, in C-peptide positive type 1 diabetes patients and safety experience on subcutaneous injection with the 65kDa isoform of glutamic acid decarboxylase in alum (GAD-alum) and an altered peptide ligand based on putative major autoantigenic sites in the insulin B9-23 chain, which had induced strong Th2 responses in animal models (Alleva et al., 2006; Alleva et al., 2002; Thrower & Bingley, 2009) (Table 2).

It has been observed in the Diabetes Prevention trial – Type1 (DPT-1) that oral administration of insulin in a group of patients with high IAA titers might allow an important delay in T1D onset (Skyler et al., 2005). TrialNet is now testing the efficacy of oral insulin in decreasing the chances of high-risk individuals converting to T1D (Haller et al., 2007). The immunomodulation with hsp60 has shown to provide some preservation of C-peptide in newly diagnosed adult type 1 diabetics and a significant reduction in inflammation of the pancreas with continued insulin production, suggesting that the progression of the disease may be prevented (Elias et al., 2006; Lazar et al., 2007; Raz et al., 2001). Additionally, the safety experience with subcutaneous GAD65 (Diamyd's GAD65) has been demonstrated in latent autoimmune diabetes of adulthood (LADA) patients (Agardh et al., 2005). The results indicate that this treatment increases fasting p-C-peptide concentrations after 24 weeks in subjects treated with a moderate dose (20 µg) but not in subjects treated with higher doses (100 or 500 µg) or lower doses (4 µg) (Stenström et al., 2005).

Other trials using a DNA vaccine-based approaches include BHT-3021 (Bayhill Therapeutics) (Burn, 2010), a plasmid encoding proinsulin, designed to target specific pathogenic immune cells. BHT-3021 has shown considerable effectiveness in the new-onset

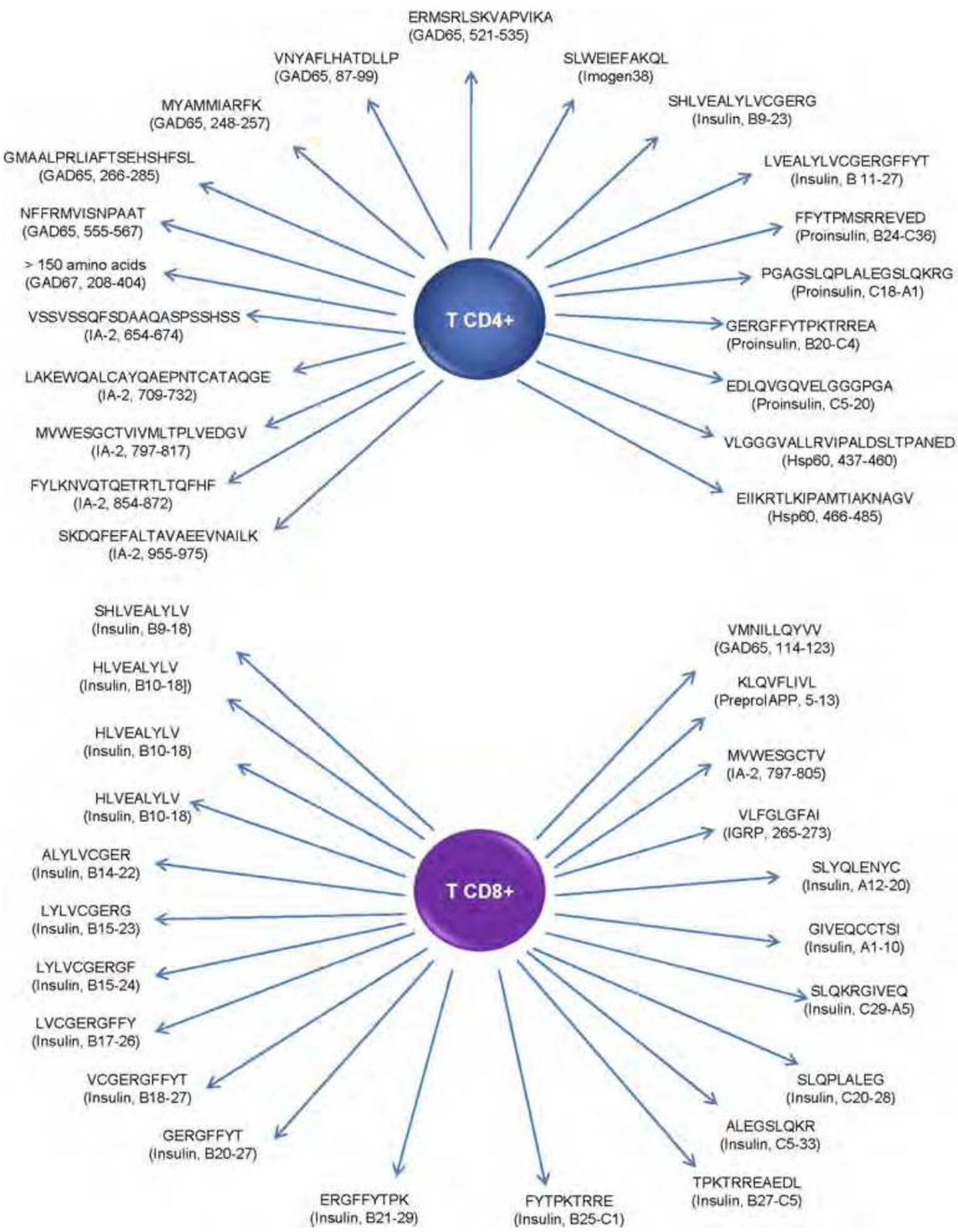

Fig. 4. CD4 and CD8 T cell epitopes for human pancreatic beta-cell antigens. *(Amino acid positions are indicated in brackets.)*

diabetes in the NOD mice. In the current phase I/II clinical trial, BHT-3021, administered by intra-muscular route, demonstrated preservation of C-peptide and an acceptable safety and tolerance in patients with T1D (Sanjeevi, 2009).

Therapeutic agent	Methodof delivery	Phase	Population targeted	ClinicalTrials.gov identifier
Insulin	O	III	RR	NCT00004984
	IN	III	CR	NCT00223613 NCT00336674
	PRT	II	RR	NCT00654121
IBC-VS01	IM	I	ND	NCT00057499
NBI-6024	SC	I	ND	NCT00873561
BHT-3021	IM	I	EP	NCT00453375
rhGAD-alum	SC	II	ND	NCT00529399 NCT01129232
DiaPep277	SC	III	ND	NCT01103284 NCT00615264 NCT00644501

Table 2. Antigen-specific tolerance-based clinical trials for type 1 diabetes. *CR: children at risk of T1D; EP: established patients; DiaPep277: Hsp60 immunodominant peptide p277; IBC-VS01: human insulin B chain in incomplete Freund's adjuvant (IFA) vaccine; IM: intramuscular; IN: intranasal; NBI-6024: altered peptide ligand (APL) insulin B9-23; ND: newly diagnosed; PRT: parenteral; rhGAD-alum: recombinant human glutamic acid decarboxylase (rhGAD65) formulated in alum; RR: relatives at risk of T1D; SC: subcutaneously; SR: subjects at risk of T1D.*

3.3 Combination immunotherapy approaches

Failure to induce a lasting complete remission in patients with T1D using any single agent suggests that combination therapies may be needed for effective prevention of the disease or reversal of new-onset T1D (Luo et al., 2010). Among these approaches that are currently being tried, combinations between immunosuppressive or anti-inflammatory and antigen-specific vaccines are of particular interest, because of their quite promising early preclinical trial results. The most potent and promising ones were schemes based on a combination of anti-CD3 treatment with GAD-alum, intranasal proinsulin peptide (Bresson et al., 2006), proinsulin DNA (BHT-3021), oral insulin or anti-inflammatory drugs (Matthews et al., 2010) (Fig. 5).

4. Conclusions

T1D results from selective autoimmune destruction of insulin-producing pancreatic islet beta-cells.

Although the cause of the disease is still not fully understood, multiple immune abnormalities, involving dysfunctional regulation of the immune system that leads to the activation of self-reactive CD4+ and CD8+ T cells as well as DCs and macrophages, are believed to be a major component behind beta-cells destruction.

Fig. 5. Main combination immunotherapies for type 1 diabetes. *A1AT: alpha 1-antitrypsin; Anakinra: IL-1RA (Amgen); ATG: anti-thymocyte globulin; ATNFA: anti-tumor necrosis factor alpha; BHT-3021: proinsulin deoxyribonucleic acid; CTB-INS plasmid: cholera toxin B chain insulin; DZB: daclizumab (anti-CD25 monoclonal antibody); GAD-ALUM: glutamic acid decarboxylase formulated in Alum (Diamyd); GLP1: glucagon-like peptide-1; MMF: mycophenolate mofetil; PGCSF: pegylated granulocyte colony stimulating factor; PRO-IP: proinsulin peptide ; Rilonacept: IL-1 Trap.*

Given that there is evidence that the inflammatory phase preceding the destruction of beta-cells may be reversible and that humoral markers of the autoimmunity are usually present many years prior to and at the time of diagnosis, various approaches are being explored in order to slow down the progression of diabetes using antigen-specific and non-antigen-specific immunotherapies. The most promising results could be based on the induction of specific immunotolerance, because of the harmful health effects that could be observed when non-antigen-specific drugs are used.
Finally, it is possible that the etiological factors may be different from one patient to another and humoral immune response would be a relatively late marker for the disease progression. Most clinical trials have therefore been hampered by the lack of cellular markers of the immune processes that cause the disease.

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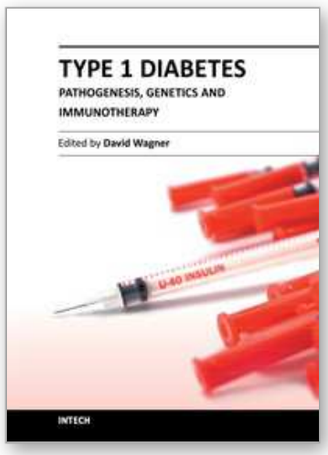

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This book is a compilation of reviews about the pathogenesis of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes. Areas including T cell development, innate immune responses, imaging of pancreata, potential viral initiators, etc. are considered.

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