Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by glucose intolerance and hyperglycemia. The clinical manifestations are the result of either absolute or relative deficiency of insulin secretion. Diabetes mellitus is a leading cause of blindness, amputations and end-stage renal disease, and is a major factor contributing to cardiovascular diseases and premature death. An expert committee of American Diabetes Association has proposed four categories of diabetes, based on aetiology of the disease. The categories are type 1 (formerly defined as insulin-dependent diabetes mellitus), type 2 (with a major component of insulin resistance, defined as non-insulin dependent diabetes mellitus), gestational diabetes a other types of diabetes (e.g. the maturity-onset diabetes of youth) [1].

Type 1A diabetes mellitus (DM 1A) is a condition caused by an autoimmune response against insulin-secreting beta cells of the pancreas resulting in their destruction. It is usually characterized by acute onset and dependence on exogenous insulin for survival.

Epidemiology of Type 1A diabetes mellitus

Current estimates indicate that autoimmune diabetes mellitus represents about 5 to 10% of the diabetes developing in adults. A recent analysis of data on published incidence trends showed that the incidence of DM 1A had been generally increasing by 3.0% per year, and it would be app. about 40% higher in 2010 than in 1998 [6].

When an individual presents with DM 1A, it indicates that he/she and his/her relatives have an increased risk of suffering from or developing a series of autoimmune disorders, such as celiac disease (app. 5% patients with DM 1A), Grawes-Basedow’s disease, Addison’s disease, pernicious anaemia or other [7, 8].

A general description of the disease process begins with a genetic susceptibility to the development of DM 1A,
a triggering event followed by autoimmune reactions that cause complete islet β cells destruction [9]. It means that the autoimmune response causing insulin is generally triggered by an environmental stimulus, but occurs primarily in those who are genetically predisposed to the disease.

Type 1A diabetes tends to run in families and there is substantial evidence that genetics plays a significant role in causing the disease [10]. Identical twins of patients with DM 1A have an overall risk of developing the disease 50%. This risk varies dramatically with the diabetic twin’s age of disease onset. If the identical twin develops diabetes after age 5, the risk for the other twin exceeds 50%. In contrast if the twin develops diabetes after age 25, the risk is less than 10%. The risk of developing diabetes is app. 5% for a sibling or an offspring of the DM 1A patient and that in common population is app. 1:300. The incidence decreases in the third decade of life to increase again in the fifth to seventh decade [11].

One of the most striking characteristics of DM 1A is large geographic variability in its incidence. Scandinavia and the Mediterranean island of Sardinia, respectively, have the highest incidence rates in the world contrary to the Oriental population with the lowest rate. A child in Finland is 400-times more likely to develop diabetes than one in China. The incidence rate of DM 1A in developed countries has been clearly rising and affecting younger children [12]. The geographical and ethnic variations in type 1A diabetes reflect the prevalence of susceptibility genes or causal environmental factors, or both [13-15].

DM 1A diagnosed in adulthood seems to be associated with male excess with a male: female ratio between 1.3 and 2.15 in most populations of European origin and there is also the pubertal peak of incidence in females [16, 17].

Genetics of type 1A diabetes mellitus

DM 1A is a genetically determined disease and many genes or genetic regions were found to be associated with its induction [for review see 18, 19]. Several genome-wide linkage studies have been conducted to identify candidate regions that may contain unidentified susceptibility genes. About 20 candidate regions for diabetes genes have been reported in linkage studies of affected sib pairs. Most of the known or suspected susceptibility loci have been designated IDDM, e.g. IDDM1 refers to genes mapping to the HLA region at 6p21, IDDM2 to the insulin region at 11p15, etc. [20] (table 1).

The genetic region of the major histocompatibility complex in man, HLA (human leukocyte antigens), is located on the short arm of chromosome 6 (p21.3) and occupies a large segment of DNA, extending about 3,600 kb (3.6 cM). It is a region of highly polymorphic genes that form separate gene clusters, class I (telomeric) and class II (centromeric). These two regions are separated by another cluster of unrelated genes called class III [21-23] (figure 1). A major determinant of genetic susceptibility to autoimmune diseases resides in the HLA class II region. HLA class II molecules, particularly DR and DQ, account for app. 40% of the genetic risk for DM 1A development. As the HLA region displays a significant degree of linkage disequilibrium (i.e. specific DQ and DR alleles are non-randomly associated with each other), associations of HLA alleles with disease must be considered as haplotype specific and not allele specific.

Individuals with the highest risk for type 1A diabetes express both predisposing haplotypes: DQA1*0501-DQBI*0201 (DQ2), which is almost always inherited with DRBI*0301 (DR3) and DQA1*0301-DQBI*0302 (DQ8), inherited with DRBI*0401 or DRBI*0402 (DR4) [24-26]. These individuals have been referred to as DR3/DR4, DQ2/DQ8 heterozygotes. Individuals who carry this high risk haplotypic combination have ~5% absolute risk of DM 1A, however within affected families, this genotype shows ~20% risk; app. 40% of diabetic children possess this

<table>
<thead>
<tr>
<th>Locus</th>
<th>Region</th>
<th>(\lambda_s)</th>
<th>LOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDDM1 (HLA)</td>
<td>6p21</td>
<td>1.7-4.2</td>
<td>65.8</td>
</tr>
<tr>
<td>IDDM2 (INS)</td>
<td>11p15</td>
<td>1.6</td>
<td>4.28</td>
</tr>
<tr>
<td>IDDM3</td>
<td>15q26</td>
<td>1.0-1.5</td>
<td>2.7</td>
</tr>
<tr>
<td>IDDM4</td>
<td>11q13</td>
<td>1.0-2.1</td>
<td>3.6</td>
</tr>
<tr>
<td>IDDM5</td>
<td>6q25</td>
<td>1.0-1.7</td>
<td>3.4</td>
</tr>
<tr>
<td>IDDM6</td>
<td>18q12-q21</td>
<td>1.0-1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>IDDM7</td>
<td>2q31</td>
<td>1.0-1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>IDDM8</td>
<td>6q27</td>
<td>1.0-2.1</td>
<td>3.6</td>
</tr>
<tr>
<td>IDDM9</td>
<td>3q22-q25</td>
<td>1.0-1.7</td>
<td>3.4</td>
</tr>
<tr>
<td>IDDM10</td>
<td>10p11-q11</td>
<td>1.1-2.2</td>
<td>2.8</td>
</tr>
<tr>
<td>IDDM11</td>
<td>14q24-q31</td>
<td>1.1-2.2</td>
<td>4.0</td>
</tr>
<tr>
<td>IDDM12 (CTLA-4)</td>
<td>2q31-q33</td>
<td>1.1-2.2</td>
<td>3.57</td>
</tr>
<tr>
<td>IDDM13*</td>
<td>2q34-q35</td>
<td>1.1-2.2</td>
<td>3.57</td>
</tr>
<tr>
<td>IDDM15</td>
<td>6q21</td>
<td>1.0-2.1</td>
<td>3.6</td>
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<tr>
<td>IDDM16 (IGH)</td>
<td>14q12</td>
<td>1.0-2.1</td>
<td>3.6</td>
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<td>IDDM17</td>
<td>10q25</td>
<td>1.0-2.1</td>
<td>3.6</td>
</tr>
<tr>
<td>IDDM18 (IL-12p40)</td>
<td>5q33</td>
<td>1.0-2.1</td>
<td>3.6</td>
</tr>
<tr>
<td>(7q25)</td>
<td>1.81</td>
<td>3.93</td>
<td></td>
</tr>
<tr>
<td>16q22-q24</td>
<td>1.6</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>8q22-q24</td>
<td>2.4</td>
<td></td>
<td></td>
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</tbody>
</table>

* The symbol IDDM14 has been reserved, but not published.
\(\lambda_s\) – lambda-s – these values reflect a sibling risk of a disease in relation to its population prevalence.

References to particular findings are available in the publication Kantarova D et al. [19]
genotype compared to 2% of children in the healthy population [20, 24, 25].

HLA-alleles have also been associated with protection from type 1A diabetes, esp. the haplotype DQA1*0102/DQB1*0602/DRB1*1501 (DQ6, DR15) confers strong protection. Evidence suggests that such protection may be mostly encoded by the DQB1*0602 allele; however, although this protective effect is extremely powerful, it is not absolute [24, 27, 28]. To summarize, as some HLA haplotypes are associated with high, moderate, low risk and even “protection”, their identification is useful in disease prediction (table 2).

There are also some reports on associations between the last group of class II HLA alleles and DM 1A. HLA-DPB1*0402 negatively associated with [29-31].
The influence of the HLA class II molecules on the risk of DM 1A is related to their central role in antigen presentation and the activation of a helper T cell mediated immune response [for a review see 22].

The second well established susceptibility locus to DM 1A is on chromosome 11p15.5, which is mapped to a region containing the variable number of tandem repeat (VNTR) polymorphism in the promoter region of the insulin gene (IDDM2). This VNTR region is categorised into classes I to III. VNTR I homozygous individuals develop DM 1A more likely than those with VNTR III; VNTRII is associated with resistance to the disease induction. VNTR I allele predispose to DM 1A by reducing tolerance to insulin and its precursors via lower insulin transcription in the thymic medullar epithelial cells [18, 32, 33].

The next DM A1 susceptibility genetic region, IDDM12, is located on the long arm of chromosome 2 (2q33) and contains the CTLA-4 (cytotoxic T lymphocyte antigen-4) gene [34, 35]. CTLA-4 plays an important role in regulation of the immune response, esp. in suppressive activities of CD+CD25+ T regulatory cells (Treg) [36].

The fourth established human DM 1A susceptibility locus is PTPN 22 (protein tyrosine phosphatase non-receptor type 22; chromosome 1p13). It encodes a lymphoid protein tyrosine kinase (LYP) that is important in negative control of T cell activation and in T cell development [37, 38].

It is well recognized that IL-2 has paradoxical functions in T cell homeostasis, acting as a potent T cell growth factor during the initiation of immune responses and having a crucial function in the termination of T cell responses and maintenance of self-tolerance. The latter function has been proposed to be due to a requirement for interleukin 2 (IL-2) signalling for the development and function of regulatory T cells. From this point of view is very interesting evidence that the region containing the gene IL2RA encoding the alpha chain of the IL-2 receptor (CD25) on chromosome 10p15-p14 could be the fifth susceptibility locus for human DM 1A [39].

IDDM4 is a region on chromosome 11q13 and one of its genes that might be involved in DM 1A genetic predisposition can be that coding for FADD, a molecule involved in the apoptosis process (40). IDDM7 on chromosome 2q31-33 may identical with NeuroD gene that is involved in morphogenesis of β cells of Langerhans’ islets [41, 42]. NRAMP1 gene is probably identical with IDDM13, a region on the long arm of chromosome 2 (2q34-35) [41]. It encodes a protein responsible form macrophage resistance to intracellular parasitic bacteria. IDDM18 (5q31.1-q33.1) is a genetic region harbouring p40 chain of interleukin 12 [43]. IL-12 drives the differentiation of T cells towards the TH1 subset and autoreactive T cell response induced by IL-12 might predispose to self-destructive immunity [44]. There is also a report on association CD4 SNP promoter polymorphism (12p) and type 1 diabetes mellitus [45]. CD4 is a principal differentiation antigen of T helper cells involved in cell cooperation and signal transduction.

### Table 2. Spectrum of diabetes risk HLA haplotypes

<table>
<thead>
<tr>
<th>High risk haplotypes</th>
<th>Moderate risk haplotypes</th>
<th>Protective haplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR3 DRB1<em>0301 DQA1</em>0501 DQB1*0201</td>
<td>DR1 DRB1<em>0101 DQA1</em>0101 DQB1*0501</td>
<td>Strong protection DR2 DRB1<em>1501 DQA1</em>0102 DQB1*0602</td>
</tr>
<tr>
<td>DR4 DRB1<em>0401 DQA1</em>0301 DQB1*0302</td>
<td>DR8 DRB1<em>0801 DQA1</em>0401 DQB1*0503</td>
<td>DR6 DRB1<em>1401 DQA1</em>0101 DQB1*0503</td>
</tr>
<tr>
<td>DRB1<em>0402 DQA1</em>0301 DQB1*0302</td>
<td>DR7 DRB1<em>0701 DQA1</em>0201 DQB1*0303</td>
<td>DR5 DRB1<em>1101 DQA1</em>0501 DQB1*0301</td>
</tr>
<tr>
<td>DRB1<em>0405 DQA1</em>0301 DQB1*0302</td>
<td></td>
<td>Moderate protection DR7 DRB1<em>0701 DQA1</em>0201 DQB1*0302</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weak protection DR7 DRB1<em>0701 DQA1</em>0201 DQB1*0201</td>
</tr>
</tbody>
</table>

There are reports on other associations and one can expect that genetic DMA-1A map will be completely filled up in the near future.

### Environmental factors in the ethiopathogenesis of Type 1A diabetes mellitus

Although DM 1A susceptibility has an apparent genetic origin, what exactly is responsible for stimulating the autoimmune response remains unclear. Various studies have shown that the concordance rate for type 1A diabetes among monozygotic twins is about 50%, meaning that environmental factors must also play a significant role. There is also some seasonal variation in the incidence of DM 1A, with more patients presenting with the disease in the fall of summer and winter months. This variation has been ascribed to potential viral infections causing beta cell destruction [46, 47].

Congenitally acquired rubella virus was the first reported to be associated with DM 1A in 1969 [48]. Rubella virus can be grown from foetal pancreas and app. 1/5 of children infected with rubella in utero progressed to DM
autoimmunity may be responsible for DM 1A following β rubella-associated DM 1A remains therefore unresolved. The mechanism of rubella-associated DM 1A remains therefore unresolved. Early direct infection, perhaps resulting in a breakdown of β cells differentiation during foetal development and not autoimmunity may be responsible for DM 1A following congenital rubella.

Mumps epidemics have been associated with an increase in incidence of DM 1A [51], and the parotitis virus was shown to infect human β cells in vitro [52]. However, similarly as with rubella, the mumps vaccination has not been associated with development of islet antibodies. Mumps virus-associated DM 1A remains therefore unproven [53, 54].

The association of enteroviruses (including entero-, echo- and coxsackie viruses) with DM 1A has attracted most attention when reported that enterovirus infections had been diagnosed in 51% of cases and 28% of controls in the six months before the development of islet antibodies [55, 56]. It was suggested that these viruses could stimulate a β cell autoimmune response. The sequence of the region of GAD (amino acid residues 250-273) is significantly similar to the Cox sackie virus B4 strain p2C protein (CB4-virus) [57]. It was thought that these viruses induced activation and proliferation of T cells specific for a viral epitope that mimics a protein unique to β cells (phenomenon of molecular mimicry) causing therefore cytotoxic T cells to respond to the β cells autoantigens [46]. However, further studies have proved that enteroviruses could be potentially causal at DM 1A onset, but not at the initiation of islet autoimmunity [58, 59].

Given sparse evidence for the initiation of islet autoimmunity by enteroviruses, attention was paid to another group of RNA viruses, to rotaviruses. Rotaviruses are double-stranded RNA viruses of the reovirus family and are the predominant cause of gastroenteritis in infants. Strong sequence similarities between rotavirus VP7 and two T cell islet antigen epitopes, one in GAD65 and one in IA-2 [54] make rotaviruses very suspect from inducing autoimmune processes resulting in DM 1A; however it needs to be confirmed in further studies.

The innate immune system senses invading microorganisms by a phylogenetically conserved family of proteins – pattern recognition receptors of which Toll-like receptors (TLRs) are one of the most important [for a review see 60]. TLR3 is important in the induction of antiviral defence mechanisms. The replicative cycle of viral infections in many cases involves double-stranded RNA (dsRNA) production where dsRNA is either a by-product generated by a symmetrical transcription of DNA virus genomes or is an essential intermediate in viral RNA synthesis. dsRNA is a very potent inducer of type I interferons and other cytokines, which exert potent antiviral and immunostimulatory activities. As TLR3 is not only important in innate immunity, but is also present on β cells [61], it may be involved in mechanisms leading to autoimmune diabetes [62].

Some dietary factors may contribute to the development of diabetes too. Bovine milk ingestion, particularly in the first months of life is associated with development of the disease. One theory suggests that exposure to cow’s milk can induce an autoantibody response to proteins (e.g. p69) expressed by β cells [63]. A possible explanation of the findings can be that in genetically predisposed individuals no tolerance to cow milk proteins develops; however, the question is not resolved as antibodies to various cow milk proteins can be also detected in healthy first degree relatives.

An increase of allergy and autoimmune prevalence has occurred in “westernized” societies over the past few decades. This is therefore thought to be primarily due to changes that have taken place in the environment in developed countries as result of reducing infections during early childhood. A consequence may be a bias of the physiological development of the immune system to either Th2 (allergies) or Th1 (autoimmune disorders) direction or an insufficient activity of regulatory T cells (a hygiene hypothesis) [for reviews see 22, 64].

Autoimmune mechanisms in destruction of beta cells of pancreas

Type 1 diabetes mellitus results from an organ-specific autoimmune-mediated loss of insulin-secreting β cells of pancreas. This chronic destructive process involves both cellular and humoral components of immunity. Markers of this process are detectable in the peripheral blood months or even years before the onset of clinical diabetes [57].

The two distinctive features of type 1A diabetes are the infiltration of pancreatic islets by macrophages and lymphocytes and the presence of autoantibodies in the plasma [65]. Islet inflammation or insulitis is the hallmark lesion of DM 1A. Mononuclear cells, initially macrophages and dendritic cells, accumulate first around the islets. Subsequently, B and T cells (both helper and cytotoxic) arrive and form a periinsulitis. Insulitis occurs when macrophages and activated T cells invade the islets of Langerhans in the pancreas and attack the insulin-secreting β cells. Insulitis occurs during the pre-diabetic phase ultimately leading to the complete depletion of β cells, which is the characteristic of type 1 diabetes [3].

Infiltration of autoreactive T cells into the islets is essential for the development of diabetes. Studies performed in NOD mice have revealed that the influx of T cells into the pancreas is associated de novo formation of lymphoid follicles what is a prototypic feature of a chronic progressive inflammation. The experimental results show that the interaction between membrane lymphotoxin (LTα1β2) and its receptor (LTβR) is
Fig. 2. A schematic description of the roles of various subsets of T cells and their cytokines in β-cell destruction, leading to diabetes (adapted from Muir A et al. [74]). Islet cell proteins are presented by antigen presenting cells (APC, i.e. dendritic cells or macrophages or B cells) to naïve T<sub>0</sub> type cells in association with HLA class II molecules and other co-stimulatory molecules. These APC secrete IL-12, promoting the differentiation of T<sub>0</sub> cells to T<sub>1</sub> type cells. T<sub>1</sub> cells secrete IL-2 and IFN-γ that further stimulate macrophages or specific cytotoxic CD8<sup>+</sup> T cells leading to β-cell destruction and eventually diabetes. T cells on other hand can prevent β-cell destruction by secreting IL-4 early during the differentiation of T<sub>0</sub> cells, favouring a benign T<sub>2</sub> type response and down-regulating T<sub>1</sub> cells. IL-4 and IL-10 secreted by CD4<sup>+</sup> T<sub>2</sub> type cells and reduced IL-2 and IFN-γ secretion prevents β-cell destruction and diabetes essential for the development and maintenance of this lymphoid microenvironment. Lymphotoxin knock out mice and wild-type mice treated with LTβ receptor-immunoglobulin fusion protein (LTβR-Ig) reverse insulitis and prevents the formation of lymphoid follicles, even when insulitis is well established [66]. This effect is likely caused by a failure to induce lymphoid tissue chemokines and adhesion molecules [67].

The autoimmune process is initiated by activation of autoreactive CD4<sup>+</sup> T<sub>1</sub> cells. The primary antigenic stimulus to β-cell autoimmunity, however, remains unknown. One possibility is that T cell activation occurs within the islets, where autoantigens are presented either by β cells or by APCs in the vicinity. This seems, however, unlikely as naïve T cells circulate through peripheral lymphoid organs rather than through tissues. Another way could be an activation of T cells in the regional lymph nodes [68]. The third contingency is that potentially autoreactive T cells are first stimulated at a distant site, either in a tissue or in one of the peripheral lymphoid organs: T cells are activated by cross-reactive environmental antigens (molecular mimicry – see above) or microbial superantigens. Activated T<sub>1</sub> cells start to produce IFN-γ and IL-2; they activate cytotoxic T cells that subsequently mediate the destructive processes of insulitis. There is also a class I HLA molecules hyperexpression that can increase cell-mediated β cell destruction. Macrophages by their production of proinflammatory cytokines, esp. TNF and IL-1, may induce apoptosis that contributes to β cell demise; reactive oxygen species and nitric oxide may have an additional destructive effect [1, 22, 69] (figure 2). The resolution of severe insulitis by LTβR-Ig treatment [66] suggests that migration of inflammatory cells into the islets is a dynamic process in which these cells may constantly move in and out of the target tissue what results in continuous...
activation of autoreactive T cells by previously unrecognized autoantigens (epitope spreading) and tissue damage.

NKT cells are a population of T cells (T) that share some characteristics with natural killer (NK) cells. The key features characteristic of NKT cells include heavily biased T-cell receptor gene usage (Vα24JαQ and Vβ11, so-called Vβ24i-NKT cells), CD1d restriction and high levels of cytokine production, particularly IL-4 and IFN-γ [70]. Because of this property, NKT cells participate in regulation of the immune response; they can skew it into either Th1 or Th2 direction and so substantially contribute to the development of autoimmune processes. Really, it was found that NOD mice were numerically and functionally deficient in NKT cells well before the onset of diabetes [71, 72]. Similar findings were reported in humans, too. Wilson et al. (1998) found that the diabetic siblings had lower frequencies of NKT cells compared with their non-diabetic sibling. Moreover, all NKT clones isolated from the diabetics secreted only IFN-γ upon stimulation; in contrast, most of clones from the non-diabetic sibling and healthy persons secreted both IL-4 and IFN-γ.

The role of B cells in insulitis is undefined. Since B cells can transfer neither insulitis nor diabetes, they have been considered to fulfil a non-destructive, perhaps antigen-presenting function, in the insulitis lesion. Nevertheless, autoantibodies can be detected in the sera of patients; their appearance reflects the progression of humoral autoimmunity to β cells. But however, there is no evidence that autoantibodies play a direct role in the immunopathogenesis of DM 1A [74, 75].

Pancreatic β cell components that are recognized by autoantibodies include insulin, proinsulin, GAD65, and two protein tyrosine phosphatases, IA-2 and IA-2β, respectively. Other islet antigens include carboxypeptidase H, ICA, and GM gangliosides [3, 74].

Insulin was the first autoantigen identified in DM 1A. Antibodies against insulin (IAA) are one of the earliest clinical markers of prediabetes. The levels of IAA are associated with the rate of the autoimmune destruction of the β cells making their detection an important aspect of diagnosis and prevention [46]. Glutamic acid decarboxylase of Mr 65,000 (GAD65) is an enzyme that converts glutamate to γ-amino butyric acid (GABA). GAD65 is expressed in human β cells and is a major target autoantigen in type 1A diabetes. Antibodies to GAD65 can be detected in the sera of 75% of new-onset DM 1A patients, one-third of whom test negative for ICAs. When, however, GAD65 antibodies coexist with additional ICAs, they indicate a high risk of DM 1A [75].

The membrane-associated protein tyrosine phosphatase, IA-2, is expressed in islets, brain and pituitary gland. Some 60-75% of new-onset DM 1A patients have autoantibodies against the protein, compared with only 2% of healthy controls. Intra-islet expression of a homologous protein, IA-2β, is restricted to β cells and displays an autoreactivity that is generally a subset of IA-2-positive persons [74]. Islet cell autoantibodies recognize multiple cytosol antigens. They are identified by indirect immunofluorescence of frozen human pancreatic sections and are the most sensitive single predictor of future DM 1A. However, the ICA procedure is technically demanding and simpler procedures for detecting autoantibodies against defined autoantigens are more reproducible [74].

Treatment

Current therapy of DM 1A relies on insulin application. However, insulin cannot prevent all of the late complications of diabetes, and life expectancy can be reduced by 10 to 15 years due to serious complications including retinopathy, nephropathy, cardiovascular diseases, or neuropathy. Systemic immunosuppression, e.g. with cyclosporine A, can halt β cell destruction [1, 76]. However, the protection only lasted as long as the drug was present and moreover, extended therapy was not feasible due to side effects. A more promising attitude is an induction of immune tolerance. Really, several biological agents were developed and tested, e.g. by lymphotoxin-beta receptor immunoglobulin fusion protein [66, 77], a marine-sponge-derived glycolipid, α-galactosylceramide [78], and others. The latest, very promising, attitude was reported by Bresson et al. recently [79]. They were successful in reverting clinically overt symptoms in two murine diabetes models (NOD and RIP-LCMV-NP mice, respectively) by simulantaneous intranasal application of human proinsulin II B24-C36 peptide and intravenous administration of non-Fc-binding fully humanized IgG1 anti-CD3e monoclonal antibodies. The co-administration of both biological agents resulted in expansion of CD25+Foxp3+ and insulin-specific Tregs producing IL-10, TGF-β, and IL-4. This observation is highly relevant for future clinical studies in humans.

Conclusion

Type 1 diabetes mellitus is an autoimmune disorder characterized by the destruction of insulin-producing β-cells of the pancreatic islets of Langerhans and lack of endogenous insulin. Susceptibility to type 1 diabetes mellitus is influenced by both genetic and environmental factors. It is generally believed that the environmental agents, such as viral infections, trigger disease development in genetically susceptible individuals. Despite the great complexity and difficulties we have faced in the field of immunopathogenesis, genetics, epidemiology of DM 1A etc., the arrival of sophisticated technologies, techniques, refinement of statistical methods will surely bring new knowledge and enable better to comprehend and to treat this modern plague of the mankind.

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