Autoimmunity

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Under normal circumstances, the immune system only reacts to foreign body antigens other than itself, but when it causes an immune response to its own constituents for some reason, it is called Autoimmunity.

type 1 diabetes | T1D prediction | islet autoantibodies | HLA | gut microbiome

1. Introduction

Type 1 diabetes (T1D) is a chronic endocrine disease that results from autoimmune destruction of insulin-producing β-cells in the pancreas after the asymptomatic period of various duration [1][2][3].

The development of T1D is a heterogeneous process, usually proceeded by the appearance of islet-specific autoantibodies against β-cells structures. Among the autoantibodies which are construed as a sign of ongoing β-cells destruction, islet cell cytoplasmic autoantibodies (ICA), and biochemical autoantibodies targeted to insulin (IAA), islet antigen-2 protein (IA-2A), glutamic acid decarboxylase (GADA) and zinc transporter 8 (ZnT8A) are the best characterised [4]. The two most common autoantibodies present at seroconversion in childhood are IAA and GADA, whereas IA-2A and ZnT8A autoantibodies appear as the first ones in a relatively small proportion. However, they are all common at the diagnosis of the disease [5][6]. Later in the disease, disturbances in glucose metabolism become more common as β-cell destruction proceeds.

The age of seroconversion differs between various autoantibodies initialising the autoimmunity, reaching its peak before the age of two for IAA, whereas GADA peaks at the age of four to five years and continues to appear at a relatively high level throughout childhood [7][8][9]. The risk of T1D increases with an increasing number of positive autoantibodies [10][11][12][13]. The observed risk of T1D is time-constant for high IA-2A levels but decrease over time for IAA and GADA [14]. Detailed analysis of this complex relationship, including also ZnT8 autoantibody, is still lacking. A small percentage of genetically susceptible children with islet autoantibodies do not progress to clinical T1D [10]. Other risk factors associated with the rapidity of disease development are genetic susceptibilities, defined by the T1D-associated HLA genotypes and non-HLA associated genes [15][16], age of the appearance of autoantibodies [5], sex [17][18] and probably still unknown environmental factors [9][19]. The varying length of the asymptotic phase suggests that environmental elements change the pace of disease progression in addition to genetic factors. The progression from seroconversion to the onset of clinical T1D and progression of islet autoimmunity is also known to be associated with the higher levels of especially IAA [20] and IA-2A [20][21] but also GADA [22][23].

2. Factors Affecting the Progression of Autoimmunity

2.1. Genetic Factors Associated with the HLA Region

Although over 60 individual genetic loci have been associated with T1D in several studies [24][25][26], the polymorphisms of the HLA region remain the most significant contributors to the genetic susceptibility to T1D [27]. The HLA loci of DNA is approximately 4 Mb long and contains over 200 identified genes. The HLA region genes that are involved in the autoimmune response and are known to be linked to the progression to T1D can be divided into two categories: three genes that encode class I α-chain, (A, B and C), and three gene pairs of class II α- and β-chains (DR, DQ and DP) antigens. HLA class II loci are mapped to the centromeric end of the short arm of chromosome 6, while highly polymorphic class I loci are located at its telomeric end. Genes encoded by the class I HLA DR-DQ gene pairs can form four different types of class II molecules. The products of HLA class I and II loci genes are structurally similar molecules located on the cell surface, which function is the presentation of the peptide antigens to T lymphocytes. HLA class I antigens are responsible for CD8+ T cells presentation, while HLA class II antigens take part in a presentation to CD4+ T cells, which help B cell and CD8+ T cell responses. [28].

2.2. Genetic Factors Outside the HLA Region

Apart from the polymorphisms in the *INS* gene and few other loci: *PTPN22*, *SLC30A8* [29], and *BACH2* gene [16], no other SNP increase the risk of T1D with the odds ratio (OR) over 1.5. These findings highlight the importance of the HLA region compared to other genetic factors in the development of T1D [30]. Protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) gene polymorphism (rs2476601), is significantly associated with the progression from islet autoimmunity to clinical T1D [31] and rs45450798 in *PTPN22* is affecting the β-cell destruction early after the initial seroconversion [16]. Substitutions in the *PTPN22* gene that cause amino acid changes affect the B cells and T cells. In addition, it alters the function of immune cell signalling and impairs the function of regulatory T cells (Treg), which are essential in the pathogenesis of T1D [32][33]. Although most individual polymorphisms do not significantly predict the progression of autoimmunity, a genetic risk score (GRS) has been successfully applied to predict disease progression. GRS calculated as a weighted sum of all individual SNPs-associated risks has been reported to predict progression from islet autoimmunity to T1D in children and T1D progression pace in numerous studies [34][35][36]. Altogether, the genetic factors outside the HLA region and HLA genes are responsible for over 80% of the heritability of T1D [34][26].

2.3. Islet Cell Autoantibodies

The order of autoantibody appearance affects the disease risk [37]. In slow progressors to T1D, GADA is the most frequent islet autoantibody to appear as the first one [38][39]. In children positive for multiple autoantibodies, GADA-initiated autoimmunity has been associated with a reduced risk of progression to diabetes [40]. ZnT8A positivity at a young age has been associated with delayed progression to T1D [38]. However, children positive for IA-2A are at increased risk of the disease [40]. IA-2A autoantibodies are associated with a high risk of progression to clinical disease [21][41][42]. IAA frequently appears among the first autoantibodies or as the single autoantibody [18][41][43][44].

The association between young age at seroconversion for IAA and high risk of T1D is well-established [20][45][46]. Additionally, a strong reverse correlation between IAA levels and age at primary seroconversion has also been reported. IAA levels measured three months after seroconversion are decreasing significantly with increasing age at seroconversion, and in the case of GADA, the decrease in autoantibody level with time is less apparent. However, the age at seroconversion has not been reported to influence the levels of IA-2A as the first autoantibody [14][20][21][22][23][47].

2.4. Autoreactive and Regulatory T Cells

Autoreactive T cells are the primary mediators that are likely to contribute to the pathogenesis of T1D [48]. T-cell subsets might be useful as biomarkers of treatment efficacy in clinical trials [49]. T helper cells are increased in number before and at diagnosis of type 1 diabetes and might be helpful as biomarkers for disease prediction [50][51]. The most specific markers of Treg cells are FOXP3, CD4 and CD25. Alterations in CD4 T cells have been reported in patients with T1D. Similarly, the frequency of T helper cells has been reported to be increased in multiple autoantibody-positive children [52][53][54]. Dysregulation in Treg cells frequencies or functions may lead to the development of autoimmune diseases, including T1D [55][56]. Functional deficiencies of Treg in T1D are associated with T1D progression [57]. Changes in subsets of Treg might be related to more advanced stages of T1D progression [56]. Alterations in Treg profiles lead to the dysfunction of the immune regulatory mechanisms critical for protection from T1D-associated autoimmunity. FOXP3 is necessary for the proper function of Treg, and their dysfunction might lead to immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, which is often characterized by autoimmune enteropathy and T1D [58]. Alterations in FOXP3 Treg profiles have been associated with T1D and might serve as the potential biomarkers of the disease progression [59][60][61].

2.5. Environmental Risk Factors

In T1D, various environmental factors can result in the progressive loss of β-cell function that manifests clinically as hyperglycaemia. T1D is an autoimmune disease caused by an interplay of genetic and environmental factors. Several genetic risk and protective factors, mainly associated with the HLA genotypes, have been identified using genome-wide association studies during the past decades. It was speculated that the genetic predispositions of an individual solely drive the progression of autoimmunity. However, genetic predisposition alone is not sufficient to explain the increase in the prevalence of T1D since the 1950s. Several hypotheses propose an explanation for the rise in the prevalence of T1D [62][63][64]. Additional environmental factors explain the increase in frequencies of class II HLA genotypes in the general population in recent years [65][66].

2.6. Gut Microflora

Changes in the taxonomic composition of the gut microbiome precede the appearance of islet autoimmunity [67]. These taxonomic changes in the gut microbiome composition result in the decreased diversity of gut microbes in T1D. Children that are positive for at least one islet cell autoantibody and those who later during the follow-up progress to T1D have a higher *Bacteroidetes/Firmicutes* ratio and lower Shannon diversity index of the gut

microbiome compared to the healthy individuals [68][69]. Similarly, decreased diversity of gut microflora was observed when autoantibody-positive children *before* and *after* the onset of clinical T1D were compared [70]. A higher abundance of *Bacteroides* is common in children positive for at least one islet cell autoantibody [71], and progressors to T1D [72][73]. Data coming from the longitude follow-up studies demonstrate that alterations in the gut microbiome, which can be independently affected by multiple factors, are associated with the early development of islet cell autoantibodies [74]. It is being speculated that chronic fluctuating changes in the taxonomic composition of gut microflora could lead to system dysregulation and trigger immune responses, which lead to the progression to autoimmunity. However, this hypothesis has not been confirmed.

2.7. Viral Infections

Several pathogens, especially viruses, may be involved in the progression of autoimmunity and T1D development. Some studies have shown that viral infections, mainly those by enteroviruses, could be involved in the pathogenesis of T1D. Because of the molecular mimicry of human islet cell autoantigens, Coxsackie B virus and enteroviruses, which could be found in the pancreatic islets of most patients with T1D, could speed up the disease progression through the activation of the immune system [75][76][77][78]. The enteroviruses may also cause an acute infection of the pancreatic β-cells, resulting in β-cell destruction and progression to clinical T1D [79].

2.8. Dietary Factors

Diet is another environmental factor that affects the progression from islet autoimmunity to clinical T1D. Early exposure to cow's milk is associated with more rapid progression to T1D. One hypothesis explaining the role of cow's milk in disease progression is albumin's molecular mimicry to ICA, a surface protein of pancreatic β-cells [80]. High consumption of cow's milk in childhood has been associated with an increased risk of progression from islet autoimmunity to T1D [81][82][83]. The effect of hydrolysed infant formula versus conventional formula on the risk of T1D was studied in the TRIGR Randomized Clinical Trial [84]. However, no effect of the hydrolysed infant formula consumption on the risk of T1D was found.

3. Conclusions

Islet cell autoantibodies can only be measured at a certain stage of disease progression, at which the humoral autoimmunity has already been engaged. Thus, novel approaches besides traditional screening methods are required to predict the disease onset accurately, before the first signs of islet cell autoantibodies appear. Changes in the taxonomic composition of the gut microbiome, which are currently studied in children as potential biomarkers of T1D, precede the appearance of islet autoimmunity

Identifying factors leading to the destruction of β-cells offers potential means for intervention aimed at preventing T1D. It is already possible to manipulate the spontaneous appearance of islet autoantibodies by dietary modification early in life.

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