Autoimmunity

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.

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.

References

1. Atkinson, M.A.; Eisenbarth, G.S.; Michels, A.W. Type 1 diabetes. Lancet 2014, 383, 69–82.

2. Paschou, S.A.; Papadopoulou-Marketou, N.; Chrousos, G.P.; Kanaka-Gantenbein, C. On type 1 diabetes mellitus pathogenesis. Endocr. Connect. 2018, 7, R38–R46.

3. Battaglia, M.; Ahmed, S.; Anderson, M.S.; Atkinson, M.A.; Becker, D.; Bingley, P.J.; Bosi, E.; Brusko, T.M.; DiMeglio, L.A.; Evans-Molina, C.; et al. Introducing the Endotype Concept to Address the Challenge of Disease Heterogeneity in Type 1 Diabetes. Diabetes Care 2020, 43, 5–12.

4. Sosenko, J.M. Staging the progression to type 1 diabetes with prediagnostic markers. Curr. Opin. Endocrinol. Diabetes Obes. 2016, 23, 297–305.

5. Bauer, W.; Veijola, R.; Lempainen, J.; Kiviniemi, M.; Härkönen, T.; Toppari, J.; Knip, M.; Gyenesei, A.; Ilonen, J. Age at Seroconversion, HLA Genotype, and Specificity of Autoantibodies in Progression of Islet Autoimmunity in Childhood. J. Clin. Endocrinol. Metab. 2019, 104, 4521–4530.

6. Ilonen, J.; Lempainen, J.; Hammais, A.; Laine, A.P.; Härkönen, T.; Toppari, J.; Veijola, R.; Knip, M. Primary islet autoantibody at initial seroconversion and autoantibodies at diagnosis of type 1 diabetes as markers of disease heterogeneity. Pediatr. Diabetes 2018, 19, 284–292.

7. Ilonen, J.; Hammais, A.; Laine, A.-P.; Lempainen, J.; Vaarala, O.; Veijola, R.; Simell, O.; Knip, M. Patterns of β-cell autoantibody appearance and genetic associations during the first years of life. Diabetes 2013, 62, 3636–3640.

8. Giannopoulou, E.Z.; Winkler, C.; Chmiel, R.; Matzke, C.; Scholz, M.; Beyerlein, A.; Achenbach, P.; Bonifacio, E.; Ziegler, A.-G. Islet autoantibody phenotypes and incidence in children at increased risk for type 1 diabetes. Diabetologia 2015, 58, 2317–2323.

9. Krischer, J.P.; Lynch, K.F.; Lernmark, Å.; Hagopian, W.A.; Rewers, M.J.; She, J.-X.; Toppari, J.; Ziegler, A.-G.; Akolkar, B. Genetic and Environmental Interactions Modify the Risk of Diabetes-Related Autoimmunity by 6 Years of Age: The TEDDY Study. Diabetes Care 2017, 40, 1194–1202.

10. Kukko, M.; Kimpimäki, T.; Korhonen, S.; Kupila, A.; Simell, S.; Veijola, R.; Simell, T.; Ilonen, J.; Simell, O.; Knip, M. Dynamics of diabetes-associated autoantibodies in young children with human leukocyte antigen-conferred risk of type 1 diabetes recruited from the general population. J. Clin. Endocrinol. Metab. 2005, 90, 2712–2717.

11. Verge, C.F.; Gianani, R.; Kawasaki, E.; Yu, L.; Pietropaolo, M.; Chase, H.P.; Eisenbarth, G.S. Number of autoantibodies (against insulin, GAD or ICA512/IA2) rather than particular autoantibody specificities determines risk of type I diabetes. J. Autoimmun. 1996, 9, 379–383.

12. Siljander, H.T.A.; Simell, S.; Hekkala, A.; Lähde, J.; Simell, T.; Vähäsalo, P.; Veijola, R.; Ilonen, J.; Simell, O.; Knip, M. Predictive characteristics of diabetes-associated autoantibodies among children with HLA-conferred disease susceptibility in the general population. Diabetes 2009, 58, 2835–2842.

13. Bingley, P.J.; Gale, E.A.M. Progression to type 1 diabetes in islet cell antibody-positive relatives in the European Nicotinamide Diabetes Intervention Trial: The role of additional immune, genetic and metabolic markers of risk. Diabetologia 2006, 49, 881–890.

14. Köhler, M.; Beyerlein, A.; Vehik, K.; Greven, S.; Umlauf, N.; Lernmark, Å.; Hagopian, W.A.; Rewers, M.; She, J.X.; Toppari, J.; et al. Joint modeling of longitudinal autoantibody patterns and progression to type 1 diabetes: Results from the TEDDY study. Acta Diabetol. 2017, 54, 1009–1017.

15. Pociot, F.; Lernmark, Å. Genetic risk factors for type 1 diabetes. Lancet 2016, 387, 2331–2339.

16. Lempainen, J.; Laine, A.-P.; Hammais, A.; Toppari, J.; Simell, O.; Veijola, R.; Knip, M.; Ilonen, J. Non-HLA gene effects on the disease process of type 1 diabetes: From HLA susceptibility to overt disease. J. Autoimmun. 2015, 61, 45–53.

17. Turtinen, M.; Härkönen, T.; Parkkola, A.; Ilonen, J.; Knip, M. Sex as a determinant of type 1 diabetes at diagnosis. Pediatric Diabetes 2018, 19, 1221–1228.

18. Krischer, J.P.; Lynch, K.F.; Schatz, D.A.; Ilonen, J.; Lernmark, Å.; Hagopian, W.A.; Rewers, M.J.; She, J.-X.; Simell, O.G.; Toppari, J.; et al. The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: The TEDDY study. Diabetologia 2015, 58, 980–987.

19. Regnell, S.E.; Lernmark, Å. Early prediction of autoimmune (type 1) diabetes. Diabetologia 2017, 60, 1370–1381.

20. Parikka, V.; Näntö-Salonen, K.; Saarinen, M.; Simell, T.; Ilonen, J.; Hyöty, H.; Veijola, R.; Knip, M.; Simell, O. Early Seroconversion and rapidly increasing autoantibody concentrations predict prepubertal manifestation of type 1 diabetes in Children at genetic risk. Diabetologia 2012, 55, 1926–1936.

21. Achenbach, P.; Warncke, K.; Reiter, J.; Naserke, H.E.; Williams, A.J.K.; Bingley, P.J.; Bonifacio, E.; Ziegler, A.G. Stratification of Type 1 Diabetes Risk on the Basis of Islet Autoantibody Characteristics. Diabetes 2004, 53, 384–392.

22. Bingley, P.J.; Boulware, D.C.; Krischer, J.P. The implications of autoantibodies to a single islet antigen in relatives with normal glucose tolerance: Development of other autoantibodies and progression to type 1 diabetes. Diabetologia 2016, 59, 542–549.

23. Mayr, A.; Schlosser, M.; Grober, N.; Kenk, H.; Ziegler, A.G.; Bonifacio, E.; Achenbach, P. GAD autoantibody affinity and epitope specificity identify distinct immunization profiles in children at risk for type 1 diabetes. Diabetes 2007, 56, 1527–1533.

24. Redondo, M.J.; Steck, A.K.; Pugliese, A. Genetics of type 1 diabetes. Pediatric Diabetes 2018, 19, 346–353.

25. Bakay, M.; Pandey, R.; Grant, S.F.A.; Hakonarson, H. The Genetic Contribution to Type 1 Diabetes. Curr. Diab. Rep. 2019, 19, 1–14.

26. Barrett, J.C.; Clayton, D.G.; Concannon, P.; Akolkar, B.; Cooper, J.D.; Erlich, H.A.; Julier, C.; Morahan, G.; Nerup, J.; Nierras, C.; et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nat. Genet. 2009, 41, 703–707.

27. Noble, J.A.; Erlich, H.A. Genetics of type 1 diabetes. Cold Spring Harb. Perspect. Med. 2012, 2, a007732.

28. Swain, S.L.; McKinstry, K.K.; Strutt, T.M. Expanding roles for CD4+ T cells in immunity to viruses. Nat. Rev. Immunol. 2012, 12, 136–148.

29. Achenbach, P.; Lampasona, V.; Landherr, U.; Koczwara, K.; Krause, S.; Grallert, H.; Winkler, C.; Pflüger, M.; Illig, T.; Bonifacio, E.; et al. Autoantibodies to zinc transporter 8 and SLC30A8 genotype stratify type 1 diabetes risk. Diabetologia 2009, 52, 1881–1888.

30. Pociot, F.; Akolkar, B.; Concannon, P.; Erlich, H.A.; Julier, C.; Morahan, G.; Nierras, C.R.; Todd, J.A.; Rich, S.S.; Nerup, J. Genetics of type 1 diabetes: What's next? Diabetes 2010, 59, 1561–1571.

31. Lempainen, J.; Hermann, R.; Veijola, R.; Simell, O.; Knip, M.; Ilonen, J. Effect of the PTPN22 and INS risk genotypes on the progression to clinical type 1 diabetes after the initiation of β-cell autoimmunity. Diabetes 2012, 61, 963–966.

32. Bottini, N.; Peterson, E.J. Tyrosine phosphatase PTPN22: Multifunctional regulator of immune signaling, development, and disease. Annu. Rev. Immunol. 2014, 32, 83–119.

33. Valta, M.; Gazali, A.M.; Viisanen, T.; Ihantola, E.-L.; Ekman, I.; Toppari, J.; Knip, M.; Veijola, R.; Ilonen, J.; Lempainen, J.; et al. Type 1 diabetes linked PTPN22 gene polymorphism is associated with the frequency of circulating regulatory T cells. Eur. J. Immunol. 2020, 50, 581–588.

34. Redondo, M.J.; Geyer, S.; Steck, A.K.; Sharp, S.; Wentworth, J.M.; Weedon, M.N.; Antinozzi, P.; Sosenko, J.; Atkinson, M.; Pugliese, A.; et al. A Type 1 Diabetes Genetic Risk Score Predicts Progression of Islet Autoimmunity and Development of Type 1 Diabetes in Individuals at Risk. Diabetes Care 2018, 41, 1887–1894.

35. Beyerlein, A.; Bonifacio, E.; Vehik, K.; Hippich, M.; Winkler, C.; Frohnert, B.I.; Steck, A.K.; Hagopian, W.A.; Krischer, J.P.; Lernmark, Å.; et al. Progression from islet autoimmunity to clinical type 1 diabetes is influenced by genetic factors: Results from the prospective TEDDY study. J. Med. Genet. 2019, 56, 602–605.

36. Steck, A.K.; Dong, F.; Wong, R.; Fouts, A.; Liu, E.; Romanos, J.; Wijmenga, C.; Norris, J.M.; Rewers, M.J. Improving prediction of type 1 diabetes by testing non-HLA genetic variants in addition to HLA markers. Pediatric Diabetes 2014, 15, 355–362.

37. Kupila, A.; Keskinen, P.; Simell, T.; Erkkilä, S.; Arvilommi, P.; Korhonen, S.; Kimpimäki, T.; Sjöroos, M.; Ronkainen, M.; Ilonen, J.; et al. Genetic risk determines the emergence of diabetes-associated autoantibodies in young children. Diabetes 2002, 51, 646–651.

38. Long, A.E.; Wilson, I.V.; Becker, D.J.; Libman, I.M.; Arena, V.C.; Wong, F.S.; Steck, A.K.; Rewers, M.J.; Yu, L.; Achenbach, P.; et al. Characteristics of slow progression to diabetes in multiple islet autoantibody-positive individuals from five longitudinal cohorts: The SNAIL study. Diabetologia 2018, 61, 1484–1490.

39. Achenbach, P.; Hummel, M.; Thümer, L.; Boerschmann, H.; Höfelmann, D.; Ziegler, A.G. Characteristics of rapid vs slow progression to type 1 diabetes in multiple islet autoantibody-positive children. Diabetologia 2013, 56, 1615–1622.

40. Jacobsen, L.M.; Bocchino, L.; Evans-Molina, C.; DiMeglio, L.; Goland, R.; Wilson, D.M.; Atkinson, M.A.; Aye, T.; Russell, W.E.; Wentworth, J.M.; et al. The risk of progression to type 1 diabetes is highly variable in individuals with multiple autoantibodies following screening. Diabetologia 2020, 63, 588–596.

41. Kimpimäki, T.; Kulmala, P.; Savola, K.; Kupila, A.; Korhonen, S.; Simell, T.; Ilonen, J.; Simell, O.; Knip, M. Natural history of beta-cell autoimmunity in young children with increased genetic susceptibility to type 1 diabetes recruited from the general population. J. Clin. Endocrinol. Metab. 2002, 87, 4572–4579.

42. Decochez, K.; De Leeuw, I.H.; Keymeulen, B.; Mathieu, C.; Rottiers, R.; Weets, I.; Vandemeulebroucke, E.; Truyen, I.; Kaufman, L.; Schuit, F.C.; et al. IA-2 autoantibodies predict impending Type I diabetes in siblings of patients. Diabetologia 2002, 45, 1658–1666.

43. Kimpimäki, T.; Kupila, A.; Hämäläinen, A.-M.; Kukko, M.; Kulmala, P.; Savola, K.; Simell, T.; Keskinen, P.; Ilonen, J.; Simell, O.; et al. The First Signs of β-Cell Autoimmunity Appear in Infancy in Genetically Susceptible Children from the General Population: The Finnish Type 1 Diabetes Prediction and Prevention Study. J. Clin. Endocrinol. Metab. 2001, 86, 4782–4788.

44. Ziegler, A.G.; Hummel, M.; Schenker, M.; Bonifacio, E. Autoantibody appearance and risk for development of childhood diabetes in offspring of parents with type 1 diabetes: The 2-year analysis of the German BABYDIAB Study. Diabetes 1999, 48, 460–468.

45. Steck, A.K.; Johnson, K.; Barriga, K.J.; Miao, D.; Yu, L.; Hutton, J.C.; Eisenbarth, G.S.; Rewers, M.J. Age of islet autoantibody appearance and mean levels of insulin, but not GAD or IA-2 autoantibodies, predict age of diagnosis of type 1 diabetes: Diabetes autoimmunity study in the young. Diabetes Care 2011, 34, 1397–1399.

46. Hummel, M.; Bonifacio, E.; Schmid, S.; Walter, M.; Knopff, A.; Ziegler, A.-G. Brief communication: Early appearance of islet autoantibodies predicts childhood type 1 diabetes in offspring of diabetic parents. Ann. Intern. Med. 2004, 140,

882–886.

47. Siljander, H.T.; Hermann, R.; Hekkala, A.; Lahde, J.; Tanner, L.; Keskinen, P.; Ilonen, J.; Simell, O.; Veijola, R.; Knip, M. Insulin secretion and sensitivity in the prediction of type 1 diabetes in children with advanced b-cell autoimmunity. Eur. J. Endocrinol. 2013, 169, 479–485.

48. Burrack, A.L.; Martinov, T.; Fife, B.T. T Cell-Mediated Beta Cell Destruction: Autoimmunity and Alloimmunity in the Context of Type 1 Diabetes. Front. Endocrinol. 2017, 8, 343.

49. Herold, K.C.; Bundy, B.N.; Long, S.A.; Bluestone, J.A.; DiMeglio, L.A.; Dufort, M.J.; Gitelman, S.E.; Gottlieb, P.A.; Krischer, J.P.; Linsley, P.S.; et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. N. Engl. J. Med. 2019, 381, 603–613.

50. Viisanen, T.; Ihantola, E.-L.; Näntö-Salonen, K.; Hyöty, H.; Nurminen, N.; Selvenius, J.; Juutilainen, A.; Moilanen, L.; Pihlajamäki, J.; Veijola, R.; et al. Circulating CXCR5+PD-1+ICOS+ Follicular T Helper Cells Are Increased Close to the Diagnosis of Type 1 Diabetes in Children With Multiple Autoantibodies. Diabetes 2017, 66, 437–447.

51. Ekman, I.; Ihantola, E.-L.; Viisanen, T.; Rao, D.A.; Näntö-Salonen, K.; Knip, M.; Veijola, R.; Toppari, J.; Ilonen, J.; Kinnunen, T. Circulating CXCR5(-)PD-1(hi) peripheral T helper cells are associated with progression to type 1 diabetes. Diabetologia 2019, 62, 1681–1688.

52. Ferreira, R.C.; Simons, H.Z.; Thompson, W.S.; Cutler, A.J.; Dopico, X.C.; Smyth, D.J.; Mashar, M.; Schuilenburg, H.; Walker, N.M.; Dunger, D.B.; et al. IL-21 production by CD4+ effector T cells and frequency of circulating follicular helper T cells are increased in type 1 diabetes patients. Diabetologia 2015, 58, 781–790.

53. Schwedhelm, K.; Thorpe, J.; Murray, S.A.; Gavin, M.; Speake, C.; Greenbaum, C.; Cerosaletti, K.; Buckner, J.; Long, S.A. Attenuated IL-2R signaling in CD4 memory T cells of T1D subjects is intrinsic and dependent on activation state. Clin. Immunol. 2017, 181, 67–74.

54. Insel, R.; Dutta, S.; Hedrick, J. Type 1 Diabetes: Disease Stratification. Biomed. Hub 2017, 2, 111–126.

55. Grant, C.R.; Liberal, R.; Mieli-Vergani, G.; Vergani, D.; Longhi, M.S. Regulatory T-cells in autoimmune diseases: Challenges, controversies and--yet--unanswered questions. Autoimmun. Rev. 2015, 14, 105–116.

56. Viisanen, T.; Gazali, A.M.; Ihantola, E.-L.; Ekman, I.; Näntö-Salonen, K.; Veijola, R.; Toppari, J.; Knip, M.; Ilonen, J.; Kinnunen, T. FOXP3+ Regulatory T Cell Compartment Is Altered in Children With Newly Diagnosed Type 1 Diabetes but Not in Autoantibody-Positive at-Risk Children. Front. Immunol. 2019, 10, 19.

57. Lindley, S.; Dayan, C.M.; Bishop, A.; Roep, B.O.; Peakman, M.; Tree, T.I.M. Defective suppressor function in CD4(+)CD25(+) T-cells from patients with type 1 diabetes. Diabetes 2005, 54, 92–99.

58. Barzaghi, F.; Passerini, L.; Bacchetta, R. Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome: A paradigm of immunodeficiency with autoimmunity. Front. Immunol. 2012, 3, 211.

59. Hull, C.M.; Peakman, M.; Tree, T.I.M. Regulatory T cell dysfunction in type 1 diabetes: What's broken and how can we fix it? Diabetologia 2017, 60, 1839–1850.

60. Pesenacker, A.M.; Wang, A.Y.; Singh, A.; Gillies, J.; Kim, Y.; Piccirillo, C.A.; Nguyen, D.; Haining, W.N.; Tebbutt, S.J.; Panagiotopoulos, C.; et al. A Regulatory T-Cell Gene Signature Is a Specific and Sensitive Biomarker to Identify Children with New-Onset Type 1 Diabetes. Diabetes 2016, 65, 1031–1039.

61. Hundhausen, C.; Roth, A.; Whalen, E.; Chen, J.; Schneider, A.; Long, S.A.; Wei, S.; Rawlings, R.; Kinsman, M.; Evanko, S.P.; et al. Enhanced T cell responses to IL-6 in type 1 diabetes are associated with early clinical disease and increased IL-6 receptor expression. Sci. Transl. Med. 2016, 8, 356ra119.

62. Rook, G.A.W. Hygiene hypothesis and autoimmune diseases. Clin. Rev. Allergy Immunol. 2012, 42, 5–15.

63. Wilkin, T.J. The accelerator hypothesis: Weight gain as the missing link between Type I and Type II diabetes. Diabetologia 2001, 44, 914–922.

64. Dahlquist, G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. Diabetologia 2006, 49, 20–24.

65. Hermann, R.; Knip, M.; Veijola, R.; Simell, O.; Laine, A.P.; Åkerblom, H.K.; Groop, P.H.; Forsblom, C.; Pettersson-Fernholm, K.; Ilonen, J. Temporal changes in the frequencies of HLA genotypes in patients with Type 1 diabetes—Indication of an increased environmental pressure? Diabetologia 2003, 46, 420–425.

66. Ilonen, J.; Lempainen, J.; Veijola, R. The heterogeneous pathogenesis of type 1 diabetes mellitus. Nat. Rev. Endocrinol. 2019, 15, 635–650.

67. Alkanani, A.K.; Hara, N.; Gottlieb, P.A.; Ir, D.; Robertson, C.E.; Wagner, B.D.; Frank, D.N.; Zipris, D. Alterations in Intestinal Microbiota Correlate With Susceptibility to Type 1 Diabetes. Diabetes 2015, 64, 3510–3520.

68. Knip, M.; Honkanen, J. Modulation of Type 1 Diabetes Risk by the Intestinal Microbiome. Curr. Diabetes Rep. 2017, 17, 1–8.

69. Giongo, A.; Gano, K.A.; Crabb, D.B.; Mukherjee, N.; Novelo, L.L.; Casella, G.; Drew, J.C.; Ilonen, J.; Knip, M.; Hyöty, H.; et al. Toward defining the autoimmune microbiome for type 1 diabetes. ISME J. 2011, 5, 82–91.

70. Kostic, A.D.; Gevers, D.; Siljander, H.; Vatanen, T.; Hyötyläinen, T.; Hämäläinen, A.-M.; Peet, A.; Tillmann, V.; Pöhö, P.; Mattila, I.; et al. The dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes. Cell Host Microbe 2015, 17, 260–273.

71. De Goffau, M.C.; Luopajärvi, K.; Knip, M.; Ilonen, J.; Ruohtula, T.; Härkönen, T.; Orivuori, L.; Hakala, S.; Welling, G.W.; Harmsen, H.J.; et al. Fecal microbiota composition differs between children with β-cell autoimmunity and those without. Diabetes 2013, 62, 1238–1244.

72. Davis-Richardson, A.G.; Ardissone, A.N.; Dias, R.; Simell, V.; Leonard, M.T.; Kemppainen, K.M.; Drew, J.C.; Schatz, D.; Atkinson, M.A.; Kolaczkowski, B.; et al. Bacteroides dorei dominates gut microbiome prior to autoimmunity in Finnish children at high risk for type 1 diabetes. Front. Microbiol. 2014, 5, 678.

73. De Goffau, M.C.; Fuentes, S.; van den Bogert, B.; Honkanen, H.; de Vos, W.M.; Welling, G.W.; Hyöty, H.; Harmsen, H.J.M. Aberrant gut microbiota composition at the onset of type 1 diabetes in young children. Diabetologia 2014, 57, 1569–1577.

74. Endesfelder, D.; Engel, M.; Davis-Richardson, A.G.; Ardissone, A.N.; Achenbach, P.; Hummel, S.; Winkler, C.; Atkinson, M.; Schatz, D.; Triplett, E.; et al. Towards a functional hypothesis relating anti-islet cell autoimmunity to the dietary impact on microbial communities and butyrate production. Microbiome 2016, 4, 1–12.

75. Kaufman, D.L.; Erlander, M.G.; Clare-Salzler, M.; Atkinson, M.A.; Maclaren, N.K.; Tobin, A.J. Autoimmunity to two forms of glutamate decarboxylase in insulin-dependent diabetes mellitus. J. Clin. Investig. 1992, 89, 283–292.

76. Yoon, J.W.; Onodera, T.; Notkins, A.L. Virus-induced diabetes mellitus. XV. Beta cell damage and insulin-dependent hyperglycemia in mice infected with coxsackie virus B4. J. Exp. Med. 1978, 148, 1068–1080.

77. Krogvold, L.; Edwin, B.; Buanes, T.; Frisk, G.; Skog, O.; Anagandula, M.; Korsgren, O.; Undlien, D.; Eike, M.C.; Richardson, S.J.; et al. Detection of a low-grade enteroviral infection in the islets of langerhans of living patients newly diagnosed with type 1 diabetes. Diabetes 2015, 64, 1682–1687.

78. Ylipaasto, P.; Klingel, K.; Lindberg, A.M.; Otonkoski, T.; Kandolf, R.; Hovi, T.; Roivainen, M. Enterovirus infection in human pancreatic islet cells, islet tropism in vivo and receptor involvement in cultured islet beta cells. Diabetologia 2004, 47, 225–239.

79. Hyöty, H.; Leon, F.; Knip, M. Developing a vaccine for type 1 diabetes by targeting coxsackievirus B. Expert Rev. Vaccines 2018, 17, 1071–1083.

80. Luopajärvi, K.; Savilahti, E.; Virtanen, S.M.; Ilonen, J.; Knip, M.; Akerblom, H.K.; Vaarala, O. Enhanced levels of cow's milk antibodies in infancy in children who develop type 1 diabetes later in childhood. Pediatric Diabetes 2008, 9, 434–441.

81. Virtanen, S.M.; Nevalainen, J.; Kronberg-Kippilä, C.; Ahonen, S.; Tapanainen, H.; Uusitalo, L.; Takkinen, H.-M.; Niinistö, S.; Ovaskainen, M.-L.; Kenward, M.G.; et al. Food consumption and advanced β cell autoimmunity in young children with HLA-conferred susceptibility to type 1 diabetes: A nested case-control design. Am. J. Clin. Nutr. 2012, 95, 471–478.

82. Koivusaari, K.; Syrjälä, E.; Niinistö, S.; Takkinen, H.-M.; Ahonen, S.; Åkerlund, M.; Korhonen, T.E.; Toppari, J.; Ilonen, J.; Peltonen, J.; et al. Consumption of differently processed milk products in infancy and early childhood and the risk of islet autoimmunity. Br. J. Nutr. 2020, 124, 173–180.

83. Lamb, M.M.; Miller, M.; Seifert, J.A.; Frederiksen, B.; Kroehl, M.; Rewers, M.; Norris, J.M. The effect of childhood cow's milk intake and HLA-DR genotype on risk of islet autoimmunity and type 1 diabetes: The Diabetes Autoimmunity Study in the Young. Pediatric Diabetes 2015, 16, 31–38.

84. Knip, M.; Åkerblom, H.K.; Al Taji, E.; Becker, D.; Bruining, J.; Castano, L.; Danne, T.; de Beaufort, C.; Dosch, H.-M.; Dupre, J.; et al. Effect of Hydrolyzed Infant Formula vs Conventional Formula on Risk of Type 1 Diabetes: The TRIGR Randomized Clinical Trial. JAMA 2018, 319, 38–48.