THE IMPACT OF ENVIRONMENTAL EXPOSURE IN DEVELOPMENT AND IN PROGRESSION TOWARD TYPE 1 DIABETES

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Abstract

Type 1 diabetes (T1D) is an autoimmune disease where β-cells of the pancreas are under an immune attack leading to dysfunction with hypoinsulinemia and hyperglycemia. T1D is increasing rapidly among children. The genetics have not been found to be the sole cause of the disease. Environmental factors are suggested to trigger the disease. Like early childhood infections, gut microbiota, antibiotics, vaccines, vitamin D deficiency, nutritional factors, stress, chemicals and toxins. Prenatal or early life environmental exposures can have negative effect on the immune system and the development of T1D. In this review the impact of environmental exposure in development and in progression toward T1D is illustrated and summarized. The influence of environmental factors as a trigger for T1D is still uncertain. It is assumed that environmental factors can influence the onset of T1D through impaired β-cell and immune cell functions. Several environmental factors could act together and effect the β-cell or the immune system to trigger T1D in genetically predisposed individuals. Further observational studies and experiments are required.

Introduction

T1D is considered to be an autoimmune disease (Chia et al., 2018). The last 30 years there has been an increase, by several times, in incidence of T1D. It usually occurs in childhood or adolescent (Rewers & Ludvigsson, 2016). The increase in childhood is increasing rapidly and is alarmingly high (Harjutsalo et al., 2006).

The most known hypothesis of T1D pathogenesis suggest that autoantigen are produced which activates the immune system and specific T-and B-cells leading to production of autoantibodies against islet cells autoantigen in pancreas (Wang et al., 2007). The destruction of β-cell mass together with inflammatory and metabolic suppression cause β-cell dysfunction, hypoinsulinemia and hyperglycemia (Redondo et al., 2008). It has been reported to be different types of T1D were the immune system act more aggressively in younger children resulting in less insulin secretion compared to adolescent (Leete et al., 2020).

There are several genes associated to T1D. Certain major histocompatibility complex class II genes, also called human leukocyte antigen (HLA) are most important genes associated to T1D. DQA1*0301(DQ2), DQB1*0302 (DQ8), DRB1*DR301 (DR3) and a number of D4 alleles are associated to T1D. These genes provide instructions for protein making which play a critical role in the immune system. 50% of the genetic risk is due to the HLA class II region (Clayton, 2009; Pociot & Lernmark, 2016; Todd et al., 2007). Both the genetic haplotypes HLA-DR3-DQ2 and HLA-DR4-DQ8 can be present at the same time (Pociot & Lernmark, 2016). However, many individuals do carry these genes but not everyone will develop T1D (Achenbach et al., 2005). There are several hundred genes suggested to be involved in the disease pathogenesis of T1D. All genes linked to T1D are listed in appendix 1.

Before T1D develops into a clinical disease, the symptoms are invisible (Knip, 2002). The time onset of T1D may vary, in infants and young children the aggressive pancreatic β-cell destruction may result in presentation of disease within a few months. In other individuals, the process may continue for more than 20 years before eventual clinical disease onset (Knip et al., 2010). The first signs of T1D that are detectible, is the appearance of the autoantibodies which is the first sign of emerging islet autoimmunity. Five different disease-related autoantibodies are so far suggested to predict clinical T1D: Islet cell antibodies (ICA), insulin autoantibodies (IAA), autoantibodies against the 65 kD isoform of glutamic acid decarboxylase (GADA), the protein thyrosine phosphatase related islet antigen 2 molecule, insulinoma-associated antigen (IA-2A), and zinc transporter 8 (ZnT8A) which includes the ZnT8-RWQ variants (Knip et al., 2016; Pociot & Lernmark, 2016). The first islet autoantibody may appear very early, before the age of 3 month in some infants. IAA is usually the first autoantibody to arise among very young children, followed by GADA, or maybe both at same time (Kukko et al., 2005; Pociot & Lernmark, 2016). The autoantibodies against islet antigen-2 are rarely seen in the beginning, IA-2A normally appear during the pre-diabetic period (Yu et al., 1996). When the first one of these autoantibody biomarkers appear there will still be no disease onset (Pociot & Lernmark, 2016). Having only one autoantibody positive may suggest "harmless" β-cell autoimmunity, and no disease onset (Knip & Siljander, 2008). When a second, third, or fourth autoantibody against either islet antigen-2 or ZnT8 transporter appears, there will be a disease onset. The more autoantibodies found as biomarkers, the more rapid progression to clinical onset of type 1 diabetes. Former metabolic studies have suggested that positive to autoantibody is preceded by inflammation (Oresic et al., 2008; Pflueger et al., 2011). The autoantibodies associated to the disease does not have to mean that they are involved in the pathogenesis of the β-cell dysfunction but they do represent biomarkers for the pathogenesis of the disease. The disease onset is suggested to be divided into three stages. The first phase: β-cell islet autoimmunity appears- the child has normoglycemia and

no symptoms of T1D. The second phase: β-cell autoimmunity occurs, the child has dysglycaemia and still no symptoms of T1D. The third phase: developed β-cell autoimmunity and the child has dysglycaemia and symptoms of T1D (Pociot & Lernmark, 2016).

Despite this, the genetics alone do not contribute to T1D. Only 13-33 % of monozygotic twins are pairwise concordant for T1D (Kaprio et al., 1992). There is also evidence that high-risk HLA genotype has decreased over the last decades in patients with newly diagnosed T1D. At the same time the incidence of patients diagnosed with T1D carrying a low or protective HLA genotype has increased (Gillespie et al., 2004; Hermann et al., 2003). The highest increased incidence in the world is found in Finland (Harjutsalo et al., 2013) followed by Sweden with the second highest level of incidence (Ludvigsson, 2017). T1D is extremely variable among ethnic groups (Bessaoud et al., 2006). In Europe and Western countries, the incidence, are much higher than in Asia, although incidence in Korea has increased over the past two decades (Kim et al., 2016). Migrant studies suggest that the incidence of T1D has changed in groups who have moved from a low incidence region to a high incidence area (Gillespie et al., 2004; Hermann et al., 2003). The sharp rise of incidence in T1D during the last years (Patterson et al., 2012), in a time frame that is not due to genetic change, indicate that environment plays a crucial role in the development of T1D (Knip et al., 2005). The understanding that environmental factors contribute to the pathogenesis of T1D has been long known. Both as a trigger and potentiators of β-cell destruction (Akerblom et al., 2002; Knip et al., 2005; Peng & Hagopian, 2006; Pociot & Lernmark, 2016). Environmental factors are needed to trigger the disease onset (Pociot & Lernmark, 2016).

In this review the impact of environmental exposure in development and in progression toward T1D will be illustrated and summarized.

The immune system

It has been investigated whether viruses, infections, antibiotics, gut microbiota and vaccines play a crucial role in the progression and in the development of T1D. If they act as stressors, as triggers of islet autoimmunity or a cause that contributes to clinical disease onset and in what way might they contribute to the pathogenesis will be illustrated below.

Infections

According to the Finish DIPP study there are associations between the appearance of the first autoantibody in T1D and enterovirus infection (Lonnrot et al., 2000; Oikarinen et al., 2011). Enterovirus infection which has its highest rate in the fall and winter is also associated to increased T1D onset (Kimpimaki et al., 2001). Different Coxsackieviruses has been shown to be a likely islet autoimmunity trigger. Coxsackie virus B1 is showed to cause more infections than other Coxsackieviruses (Laitinen et al., 2014). Although, the German BABYDIAB and the American DAISY study showed no association between islet cell autoimmunity and enterovirus infections (Fuchtenbusch et al., 2001; Graves et al., 2003). The virus has been detected in patients with newly diagnosed T1D (Krogvold et al., 2015; Richardson et al., 2009). Suggested that enteroviruses infect the β-cells in patients with T1D and the infection is associated with inflammation and dysfunction with reduced insulin production compared to glucose levels (Francesco et al., 2007). However, enteroviruses might act as stressor, as a trigger of islet autoimmunity or a cause that contributes to clinical disease onset, which all is an unsolved issue (Drescher et al., 2004; Horwitz et al., 2001; Serreze et al., 2000; Stene et al., 2010). The TEDDY study reported an association between respiratory infection such as cold, influenza, sinusitis and laryngitis/ tracheitis and increased risk

of islet autoimmunity in young children. The risk was linked to winter infections (Lonnrot et al., 2000).

Gut microbiota

Another hypothesis is the role of the gut microbiotas association to T1D. The gut microbiota function is to help aid in nutrition from diet and generate energy. It also helps to keep gut epithelia intact and reduce permeability (Natividad et al., 2012). The collaboration between intestinal epithelium and bacteria promotes development of a normal immune system (Dave et al., 2012; Dominguez-Bello et al., 2011). The triggering factor(s) has not been identified, although the gut microbiota (effected by antibiotic usage, diet consumed, delivery mod and infections) in genetic predisposed individuals is believed to play a crucial role in development of T1D (Brown et al., 2011; Endesfelder et al., 2014; Giongo et al., 2011; Murri et al., 2013; Rosenbauer et al., 2008). Hypotheses suggest that T1D is triggered by transfer metabolites or cell components of the bacteria through a "leaky" gut wall and uptake by antigen presenting cells, and thereafter processing and presenting those antigen to active T cells (Gulden et al., 2015). Lack of tight junction and alteration in intestinal permeability allows bacterial toxins to access (Endesfelder et al., 2014). Even infectious agents or dietary antigens may affect the mucosal immune elements (Graves et al., 1999; Kostic et al., 2016). Bacteria produce short-chain fatty acids during breakdown of dietary fiber. Which reduce the intestinal (Marino et al., 2017; Ohata et al., 2005). Short-chain fatty acid is also reported to increase the number of T-cells (Furusawa et al., 2013; Marino et al., 2017).

Vaccines

Another hypothesis is that vaccine triggers the disease. Studies reported no association to neither islet autoimmunity (Graves et al., 1999; Hummel et al., 2000) or T1D (Jefferson & Demicheli, 1998; Offit & Hackett, 2003). No association to T1D onset due to vaccines were found (Morgan et al., 2016). It has also been investigated whether the Bacille Camille-Guerin (BCG) vaccine might reduce the incidence of islet autoimmunity in T1D. No study have so far shown an association between BCG vaccination and T1D or islet autoimmunity (Dahlquist & Gothefors, 1995; Huppmann et al., 2005; Rousseau et al., 2016). BCG vaccine has also been reported to not maintain β-cell function during the disease onset (Allen et al., 1999; Elliott et al., 1998).

Antibiotics

The use of antibiotics has been reported to effect T1D outcome in several studies (Wen et al., 2008). Antibiotic use during prenatal period was associated to acceleration of T1D onset (Hu et al., 2016; Peng et al., 2014). One study found that children born with cesarean section who were treated with broad-spectrum antibiotics, five or more times, during the first two years of life, showed an increased risk of developing T1D during the following 13 years (Moulder & Lahesmaa, 2016). Antibiotics used in early life increased the incidence of T1D in young children, which was related to birth delivery variant (Clausen et al., 2016).

The antibiotic Vancomycin increased the incidence of T1D in one study (Hu et al., 2016) although it reduced the incidence in another (Hansen et al., 2012). The differences in these studies outcome where the levels of the human intestinal mucin-degrading bacteria *Akkermansia*. High levels of *Akkermansia* has reported reduce inflammation, protect and reduce T1D incidence when exercising a gluten-free diet, due to changes in the intestinal microbiome (Hansen et al., 2014; Marietta et al., 2013). In children with early introduction to cow-milk diet and dominant

Bacteroides also showed low levels of *Akkermansia* in the gut microbiota and was associated to early autoantibody development (Endesfelder et al., 2014). It was reported to be an association of diet consumed, the microbiome and the development of autoimmunity (Endesfelder et al., 2016).

Nutritional effects

Since T1D occurs most often in young children there are several hypotheses suggesting that the first food the child is presented to might trigger T1D onset. What kind of food or supplement and the timing of the introduction may have an impact on clinical disease onset.

Vitamin D

Vitamin D plays an important role regulating genes controlling the immune system and metabolic pathways in T1D. Vitamin D has also been shown to change the T-cell response in the immune response by downregulation of T-helper cell. The seasonal pattern of increased diagnosis of T1D is suggested to be explained by the seasonal variation of the sun exposure. A study in Belgium reported that the monthly averages of sun exposed were on the contrary to the number patients newly diagnosed (Hummel et al., 2011). However, intake of vitamin D supplement has shown to decrease the risk for developing T1D. Both in late pregnancy (Sorensen et al., 2012) and in infants treated with supplements (Miettinen et al., 2012; Zipitis & Akobeng, 2008). While there are studies who have reported no association of Vitamin D intake and islet autoimmunity or increased risk of T1D (Rosenbauer et al., 2008; Simpson et al., 2011).

Gluten

Several studies have tried to investigate the association of gluten and T1D with different results. It has been shown that introduction of cereal, both containing gluten and non-gluten, are crucial for the development of islet autoimmunity specially between 4-6 month (Norris et al., 2003). The BABYDIAB study reported association with early exposure to gluten as an increased risk (Ziegler et al., 2003). ABIS reported on the other hand an increased risk with late introduction of gluten (Wahlberg et al., 2006). While the DIPP study in Finland found no association with gluten at all (Virtanen et al., 2011). Although, ABIS also reported that mothers diet during pregnancy, was an increased risk of islet autoimmunity (Brekke & Ludvigsson, 2010). Mothers kept on a gluten free diet during pregnancy decreased the incidence of T1D, and reduced insulitis in offspring (Antvorskov et al., 2016). The Danish National Birth Cohort also reported reduced risk of T1D in the children, where the mothers limited the intake of gluten during pregnancy (Antvorskov et al., 2018).

It is indicated that some individuals with T1D might have an abnormal mucosal immune response towards gluten (Troncone et al., 2003). Gliadin stimulation activates macrophages to produce proinflammatory cytokines Interleukin (IL) 6 and IL 12 (Thomas et al., 2006). It is also reported that a gluten free diet reduced the activity of natural killer cells (Larsen et al., 2014) and reduced active cytotoxic T lymphocytes (Larsen et al., 2015).

T1D and Celiac Disease have the same genetic background by sharing HLA-DQ2/DQ8 haplotypes. 10 % of those with T1D also suffered from Celiac Disease (Barera et al., 2002). Although, the risk was lower for those patients who exercised a gluten free diet (Cosnes et al., 2008).

Milk

Studies showed that breastfeeding reduced the risk for T1D development but did not protect against T1D (Norris et al., 2003; Virtanen et al., 2011; Ziegler et al., 2003). Children who were breastfeeding at the same time as they were introduced to cereals showed a reduced risk of islet autoimmunity (Norris et al., 2003) and T1D (Frederiksen et al., 2013). Children who received a casein hydrolysate formula when there was no breastmilk available showed a lower risk of islet autoimmunity than those who were given cows´ milk based formula during the first 6-8 month of life (Knip et al., 2010).

Early exposure to cows´ milk in infants showed a risk of developing T1D (Gimeno & deSouza, 1997; Virtanen et al., 1999; Virtanen et al., 1998). Although, other birth cohort studies showed no link between exposure to cows´ milk and islet autoimmunity or T1D (Frederiksen et al., 2013; Holmberg et al., 2007; Norris et al., 2003; Ziegler et al., 2003). Studies done in later childhood also showed different results with increased risk of islet autoimmunity (Virtanen et al., 2012; Wahlberg et al., 2006) and T1D (Verge et al., 1994; Virtanen et al., 2000) and one study showed a decreased risk of T1D (Rosenbauer et al., 2008).

Lamb et al. (2015) reported that individuals with islet autoimmunity, independent of genetic risk, who consumed higher intake of cow´s milk increased progression toward T1D. Which were suggested to be caused by the fatty acids linoleic acid, myristic, and monounsaturated palmitoleic acid isomers existing in milk (Virtanen et al., 2010).

The main proteins in cows´ milk are β-casein type A1 and A2 (Pal et al., 2015). Human breast milk contain only of A2 β-casein (Wada & Lonnerdal, 2015). It is a difference in the amino acid sequence between the two different types. In A1 β-casein the amino-acid histidine is present at position 67, while A2 β-casein has the amino-acid proline at the same position. The A1 β-casein histidine effects the μ-opioid receptor BCM-7 which can make crossing over the gastrointestinal wall and enter systemic circulation possible (Kost et al., 2009). No study on human has so far been performed to investigate the difference between A1 and A2 β-casein and the association to T1D. However, a study in NOD mice did show that older generation NOD mice feed with A1 β-casein doubled the incidence of T1D, compared to those feed with A2 β-casein. Fasting blood glucose levels, 2- hour glycemic load and insulitis were also higher in the NOD mice consuming A1 β-casein (Chia et al., 2018).

It is speculated as to whether bovine insulin produces antibodies. Since milk is suggested to be one of the first foreign, complex proteins that an infant is exposed to and insulin cross-reacts with bovine insulin in the insulin antibody assays. Bovine insulin differs from human insulin by three different amino acids. Two in the A chain and one in the B chain (Vaarala et al., 1999). It might trigger the immune response later be diverted into an attack against the child human insulin. In children who had developed islet autoimmunity the children also had IgG antibodies to bovine insulin (Vaarala et al., 2012).

Fatty acid

A deficiency of Omega 3 fatty acids has been suggested to trigger the inflammatory responses and might predispose inflammatory reactions. In late pregnancy there was no association found between docosahexanoic acid (DHA) and eicosapentaenoic acid (EPA), and other fatty acid concentrations and islet autoimmunity or T1D (Sorensen et al., 2012). A study in Finland reported association to increased risk of islet autoimmunity with lower concentrations of Omega 6 and especially the serum linoleic acid, but no association was found for DHA or EPA (Virtanen et al.,

2010). Although, higher omega 3 fatty acid in the membrane of the erythrocyte showed a lower risk of islet autoimmunity as well as higher omega-3 fatty acid intake during childhood (Norris et al., 2007).

Carbohydrate and sugar

It has been shown in studies that sugar intake play a role in T1D development (Dahlquist et al., 1990). In one study they investigated the food intake one year before disease onset and they found an association between high intake of energy, protein and carbohydrate with increased T1D risk. High intake of carbohydrates and specially disaccharides and sucrose were associated with increased risk. High intake of bread was also associated with increased T1D risk (Pundziute-Lycka et al., 2004). However, in this study they did not measure for islet autoimmunity. In another study where they did measure for islet autoimmunity, it was found that children who had developed islet autoimmunity were more likely to also have a high-risk HLA genotype and family history of T1D, than children who did not develop islet autoimmunity. If the child had the genotype HLA DR,DQ and history of T1D in the family, food containing higher glycemic index (GI) and glycemic load (GL) were not associated with islet autoimmunity development. No association between BMI and development of islet autoimmunity were found. Although, in children with already developed islet autoimmunity who consumed food with higher GI and GL showed to be positively associated with a more rapid progression to disease onset (Lamb et al., 2008).

Lamb et al. (2015) showed that total sugar intake was associated with an increased risk of progression to T1D in children with islet autoimmunity. Increased consumption of sugar-sweetened beverage was also associated with T1D development in children with developed islet autoimmunity who also had high genetic risk for T1D, but not for children with low/moderate genetic predisposition. These results suggest that regardless of HLA genotype, when the child developed islet autoimmunity, sugar intake increases the child risk of progression to T1D onset.

The association between total amount of sugar and the rapid progression of T1D in children with islet autoimmunity may be due to indirect or direct biological factors. Periodically exposure to high levels of dietary sugar is preliminary to be toxic for the β-cell and the sugar exposure may directly promote β-cell apoptosis and reduce normal proliferation of the β-cell (Zhang et al., 2014). Frequent hyperglycemia may also lead to β-cell apoptosis due to oxidative stress and cytokine toxicity (MandrupPoulsen, 1996; Zhang et al., 2014). Another hypothesis is that great amount of sugar intake and the rapid progression of T1D is induced by the increased insulin demands on the β-cell which already is under an autoimmune attack gets overloaded by the increased sugar intake. This overload of β-cell may lead accelerated β-cell apoptosis by making the β-cell more active and thus more visible to the immune system (Aaen et al., 1990), possibly upregulating the immune attack (Dahlquist, 2006).

Stress

Physiological and psychological stress have been shown to be linked to the development of T1D. Stress on the β-cell and different kind of stress on specific organelles with a key role in β-cell function, have been reported to have an impact on the progression and on the development of T1D.

Physiological and psychological stress

Stress is another hypothesis that contribute to T1D. Carlsson et al. (2014), showed that in high stressed children, after measuring cortisol, C-peptide, proinsulin and glucose, that stress in form of serious life event, parenting stress and trauma would cause significantly higher cortisol in the child. Although, in contrast a lower secretion of C-peptide and reversed relationship to spontaneously secreted IL-5 which stimulates cell growth and increases immunoglobulin secretion, IgA. IL-5 is also a key mediator to activating eosinophils in high stressed children. High blood glucose or proinsulin levels were not seen in high stressed children. Although glucose was inversely correlated to cortisol and positively correlated to spontaneously secreted IL-10 and CXCL10. Both of these are involved in β-cell survival, proliferation, antibody production and have several different roles in the different immune cells.

In the DiPiS study they investigated however sever life event may lead to T1D. They followed children from two month to two years. During this time, they did not measure for islet autoimmunity but for family history of T1D, genotype and the parents own experiences of different stress situations in life. No increased risk was found for T1D in the parent who had experienced sever life event during pregnancy. It was, however, increased risk for T1D in parents experienced a severe life event between birth and two year of life. Children with DQ2/8 genotype were at increased risk of developing T1D if the parents had experienced a severe life event during the child first two years. The same increased risk was found for parents experiencing unemployment, conflict in the family or a divorce during pregnancy (Lundgren et al., 2018).

β-cell stress

There is a hypothesis, the overload hypothesis, proposing β-cell stress due to factors causing increased insulin demands, which might cause an overload burden, increasing β-cell apoptosis and β-cell vulnerability and overload for the β-cell. Suggested caused by: rapid growth, puberty, infections, low physical activity, glucose overload, overweight, trauma (Lamb et al., 2008). It has been found that tragic life events like divorce or death in family might increase the risk of islet autoimmunity. Because the psychological stress lead to increased insulin resistance it also leads to increased insulin demands and secretion which increases the demands of the β-cell, although stress through increased cortisol might also directly influence the immune system and its response (Sepa et al., 2005).

ER stress of the β-cell

The endoplasmic reticulum (ER) of the β-cell are suggested to play a target for preventing β-cell death in T1D. The ER´s task is protein folding of newly synthesized secretory proteins, calcium storage, and signaling of both pro- and anti-apoptic pathways (Oslowski & Urano, 2011). When hyperglycemia occurs, the ER plays an important role in the production of insulin protein. In order to make high quality insulin the balance between ER protein load and ER folding capacity is important. To maintain the high quality insulin ER has a quality control mechanism called the unfolded protein response (UPR) (Walter & Ron, 2011). When ER stress occur there is an imbalance between ER protein load and ER folding capacity which activates the UPR to make sure the insulin quality remains high and promote insulin secretion and β-cell survival (Lipson et al., 2006). Under pathological conditions, the chronic hyperactivation of the UPR can lead to β-cell dysfunction and β-cell death. The process when β-cell autoantigen is produced remain unknown. ER stress may result in production of abnormal proteins that interact inappropriately within the immune system. Although, the β-cell autoantigens insulin, GAD65, IA-2, ZnT-8 and Chromogranin A are all produced within the ER (Sherr et al., 2008).

Calcium is an important component in the β-cell. Some stressors like hyperglycemia, free fatty acids, cytokines and thapsigargin deplete ER calcium and induce ER stress (Cardozo et al., 2005; Hara et al., 2014). High levels of ER calcium are needed to maintain correct folding and processing of proteins (Hara et al., 2014). ER dysfunction can lead to abnormal folded complexes of insulin and other native β-cell proteins which could function as autoantigens (Delong et al., 2016).

Molecular chaperones, also located in the ER and involved in the folding of proteins, is showed to activate autoimmune T cells. ER stress promotes the production of molecular chaperones. Chaperones are supposed to stay inside the cell. However, it has been shown that ER stress conditions made chaperones translocate to other locations as cytosol and the plasma membrane where it could interact with immune cells directly (Wiersma et al., 2015). Depletion of β-cells due to ER stress and induced calcium, increase the number of insulin granules which has been transferred into antigen-presenting calls (APC) for the process. Eventually increasing the risk of misfolded forms of insulin or post-translationally modified insulin (Vomund et al., 2015).

Chemicals and toxins

There are several studies investigating the chemicals association to T1D. By binding to receptors or after uptake in the cells (by pinocytosis, endocytosis or diffusion), chemicals can act directly on β-cells or immune cells. Chemicals may also change the microbiome, the hormone balance and induce epigenetic changes. Chemical exposure may lead to apoptosis, cell death, oxidative stress and impaired insulin response (Bodin et al., 2015).

Nitrites, nitrates or nitrosamines found in water were reported to be toxic for the β-cells, and were associated to T1D (Benson et al., 2010; Kostraba et al., 1992; Van Maanen et al., 1999). Studies also reported no such association (Moltchanova et al., 2004; Muntoni et al., 2006; Zhao et al., 2001). Samuelsson et al. (2011) showed that children diagnosed with T1D had consumed water with higher concentration of nitrate than children from the control group with lower concentration in their water**.** Low zinc levels in drinking water were also associated to T1D**.**

A Swedish study reported high intake of food containing nitrites, nitrates and nitrosamines were associated to T1D (Dahlquist et al., 1990).

Air pollution and exposure to ozone and sulphate in ambient air were associated to development of T1D (Hathout et al., 2006). The endothelial cells and circulating monocytes were affected which caused DNA damage and inflammation (Danielsen et al., 2011; Hathout et al., 2001).

Conclusion

Literature that supports the impact of environmental exposure in development and in progression toward T1D has been illustrated. Environmental factors may have direct toxic, dysfunctional effect on insulin producing β-cells or the immune system and effect the microbiota, the intestinal permeability, change hormone levels and induce stress. Causing an unhealthy environment within or outside effecting the pancreas. Due to lacking evidence of one single environmental factor contribute development of T1D, there is tempting to suggest that there are several mechanisms and maybe several environmental factors that contributes to disease onset. All of them or some may in the same way affect what ultimately leads to the progression and development of T1D. The environmental impact shows to increase rapid progression to clinical disease onset. Although, it

may not be the one and only sole cause for the disease, instead a finding, seen in an unhealthy environment of the β-cell. The pathogen or host responded to might be one or several. Triggered different in individuals. There are patients with findings that autoantibodies do not always precede the disease onset of T1D. Instead the disease comes first and then the appearance of autoantibodies. The autoantibodies may not be the autoantibodies that they are supposed to be. They just might be what we see, a biomarker for disease onset and diagnose. There are different autoantibodies present in children who have same disease and carry same genetic haplotype. Epigenetic changes might lead to the difference in phenotype. Further understanding the consequences of epigenetic contribution within different phenotypes are to prefer. Further opportunities might also be increased understanding of the β-cell biology, the environment within the islet and the cause to misfolded insulin. Its role, which might be, as a presenting neoantigen that initiate a β-cell specific autoimmunity in an unhealthy environment.

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Appendix 1. Genes associated to type 1 diabetes

All genes linked to type 1 diabetes. Listed by gene name, the variant, chromosome number and chromosome location (MacArthur et al., 2017).

Mapped gene	Variant	Chromosome number and location
UBASH3A	rs9976767	21:42416281
AC009135.1, RBFOX1	rs9934817	16:6086218
LINC01104	rs9653442	2:100208905
AL136961.1	rs9585056	13:99429512
LINC02649	rs947474	10:6348488
AL117190.1, MEG3, AL117190.2	rs941576	14:100839708
AL356534.1	rs9388489	6:126377573
AL078602.1	rs9356171	6:163922743
HLA-DQA1, HLA-DQB1	rs9273363	6:32658495
HLA-DQA1	rs9272346	6:32636595
HLA-DRB9	rs9268853	6:32461866
HLA-DRA	rs9268645	6:32440750
RNU6-474P, CTLA4	rs926169	2:203858029
AL603783.1, AL049612.1	rs924043	6:170063801
CD69	rs917911	12:9753255
LINC00243	rs886424	6:30814225
CTRB1, CTRB2	rs8056814	16:75218429
RASGRP1	rs8035957	15:38546063
AL391117.1	rs7871386	9:23166744
RNU6-144P, ZYXP1	rs7831697	8:137124061
SKAP2	rs7804356	7:26852046
ANKRD55	rs7731626	5:56148856

AC114977.1, AC114977.2	rs7725052	5:40487168
ADCY7	rs77150043	16:50270338
TUBB4BP5, QRFPR	rs7679475	4:121392885
CYTL1, RN7SKP113	rs7672495	4:4990640
TENM3, AC114798.1	rs7660520	4:182824168
CD226	rs763361	18:69864406
KIAA1109	rs75793288	4:122322441
SMARCE1, AC004585.2	rs757411	17:40618898
AC008691.1	rs755374	5:159402286
FCRL3, AL356276.2	rs7528684	1:157701026
IL2RB	rs743777	22:37155567
Z94721.1	rs73043122	6:166969779
BACH2	rs72928038	6:90267049
IFIH1	rs72871627	2:162280432
ASCL2, MIR4686	rs72853903	11:2177435
SMAD3	rs72743477	15:67171953
RASGRP1	rs72727394	15:38554821
AC004585.2, SMARCE1	rs7221109	17:40614034
CTRB2, CTRB1	rs7202877	16:75213347
RASGRP1, LINC02694	rs7171171	15:38614840
MIR4686, ASCL2	rs7111341	11:2191936
LINC00993, ANKRD30A	rs7100025	10:37303610
IL2RA	rs706778	10:6056986
AC034102.3, RPS26	rs705705	12:56041720
RAB5B	Rs705699	12:55991020

LURAP1L, LURAP1L-AS1	rs7042370	9:12785074
GLIS3	rs7020673	9:4291747
IL7R	rs6897932	5:35874473
INS, INS-IGF2	rs689	11:2160994
CAMSAP2	rs6691977	1:200845831
CRB1	rs6689858	1:197406337
RSBN1, PHTF1	rs6679677	1:113761186
ABO	rs657152	9:133263862
FOSL2, AC104695.3	rs6547853	2:28423934
KIAA1109	rs6534347	4:122277280
ATXN2	rs653178	12:111569952
AP001057.1, GATD3A	rs6518350	21:44201934
GLIS3	rs6476839	9:4290823
IKZF1, AC124014.1	rs62447205	7:50398132
IL21-AS1	rs62324212	4:122639784
KEAP1, PDE4A	rs62131887	19:10476920
IL2RA	rs61839660	10:6052734
SIRPG-AS1, SIRPG	rs6043409	20:1635560
FUT2	rs602662	19:48703728
AC103796.1	rs5790666	11:27778324
AC002378.1	rs5753037	22:30185733
MEG3, AL117190.2, AL117190.1	rs56994090	14:100840110
GSDMB	rs56380902	17:39910119
IL10, AL591846.1	rs55705316	1:206760172
JAZF1-AS1	rs550448	7:28189423

LMO7, AL137782.1	rs539514	13:75752146
FUT2	rs516246	19:48702915
AC004830.2	rs4948088	7:50959497
AL163932.1, LINC01550	rs4900384	14:98032614
ERAP2, AC009126.1	rs4869313	5:96888176
ACOXL	rs4849135	2:110857502
HORMAD2	rs4820830	22:30135102
NUPR1, IL27	rs4788084	16:28528527
EFR3B	rs478222	2:25078886
CD69	rs4763879	12:9757568
GPR35	rs4676410	2:240624322
DAG1	rs4625	3:49534707
KIAA1109	rs4505848	4:122211337
BTN2A3P	rs4320356	6:26423332
AP000553.1, AP000553.2	rs428595	22:21662102
AP000553.1, AP000553.2	rs428595	22:21662102
PRKD2	rs425105	19:46705224
TNFSF15	rs4246905	9:114790969
RMI2	rs416603	16:11270222
RBM17, RPL32P23	rs41295121	10:6087680
FGF3, FGF4	rs4084127	11:69781755
PRKD2	rs402072	19:46715865
AC090955.2, AC090955.1	rs3864055	3:5093886
INS, TH	rs3842727	11:2163618
INS, TH	rs3842727	11:2163618

CTSH	rs3825932	15:78943104
GATA3	rs3802604	10:8060309
UBASH3A	rs3788013	21:42421219
CLEC2D	rs3764021	12:9681032
BACH2	rs3757247	6:90247744
AC132217.2, INS-IGF2, IGF2-AS	rs3741208	11:2148544
HNRNPA1P41, JAK2	rs36051895	9:4981866
ATG16L1	rs36001488	2:233276621
IFIH1	rs35667974	2:162268127
AL031599.1	rs34884278	1:172869708
CTSH	rs34593439	15:78942615
TYK2	rs34536443	19:10352442
ATXN2, SH2B3	rs3184504	12:111446804
ICOS, CTLA4	rs3087243	2:203874196
IL10, AL591846.1	rs3024505	1:206766559
CLEC16A	rs2903692	16:11144926
GSDMB, ZPBP2	rs2872507	17:39884510
AL592464.3, AL589702.1	rs28600853	1:2863195
NCR3, UQCRHP1	rs2857595	6:31600692
RPL23AP12, AF064858.1	rs2836882	21:39094644
LINC00892, RNU6-320P	rs2807264	X:136583619
STMN3, MHENCR	rs2738774	20:63637985
GAB3	rs2664170	X:154717327
HLA-DQB1, MTCO3P1	rs2647044	6:32700133
AC080079.2	rs2611215	4:165653115

PTPN2, AP005482.2	rs2542151	18:12779948
TRIM31-AS1, TRIM31	rs2523989	6:30110498
AL137856.1, PTPN22	rs2476601	1:113834946
BCL2L15, AP4B1-AS1	rs2358994	1:113886839
TYK2	rs2304256	19:10364976
C1QTNF6	rs229541	22:37195278
C1QTNF6	rs229533	22:37191071
ERBB3	rs2292239	12:56088396
GSDMB	rs2290400	17:39909987
SIRPG	rs2281808	20:1629905
PGM1	rs2269241	1:63643100
MICA, AL645933.3	rs2251396	6:31396930
NCOA1, AC093798.1	rs2165738	2:24469940
MAGI3	rs2153977	1:113537449
FAP, IFIH1	rs2111485	2:162254026
IL18RAP, SLC9A4	rs2075184	2:102464132
IL2, IL21	rs2069762	4:122456825
ADGRL2	rs2066363	1:81771892
IFIH1	rs1990760	2:162267541
LPAR3	rs1983853	1:84845509
BTNL2, TSBP1-AS1	rs1980493	6:32395438
RMI2	rs193778	16:11257354
PTPN2	rs1893217	18:12809341
AC132217.2, IGF2-AS, INS-IGF2	rs17885785	11:2146620
PI4KA	rs178050	22:20814301

HLA-DQB1-AS1, HLA-DQB1	rs1770	6:32660056
NAA25	rs17696736	12:112049014
LRRK2	rs17466626	12:40366829
ADAD1	rs17388568	4:122408207
FSTL4	rs17166496	5:133293192
IKZF4	rs1701704	12:56018703
DNAH2	rs16956936	17:7730374
SUOX	rs1689510	12:56002984
CD226	rs1615504	18:69859408
AL356534.1	rs1578060	6:126391101
AL356534.1	rs1538171	6:126431738
MIR3681HG	rs1534422	2:12500615
CLN3	rs151234	16:28494339
ZFP36L1, MAGOH3P	rs1465788	14:68796882
AL163932.1, LINC01550	rs1456988	14:98021670
CAPSL	rs1445898	5:35910427
AFF3	rs13415583	2:100147625
SLC25A28, NKX2-3	rs1332099	10:99538694
PTPN2	rs12971201	18:12830539
ATXN2L, AC133550.2	rs12928404	16:28835925
CLEC16A	rs12927355	16:11100914
AL390879.1	rs12863738	X:136949968
IL2RA	rs12722495	10:6055320
TYK2	rs12720356	19:10359299
CFB, AL645922.1	rs1270942	6:31951083

CLEC16A	rs12708716	16:11086016
RNU6-12P, TNFRSF11B	rs12679857	8:118965098
CUX2	rs1265564	12:111270654
ACSL1, CENPU	rs12644905	4:184755529
AC138904.2, SBK1	rs12598357	16:28329624
ZMIZ1	rs1250563	10:79287626
ZPBP2, GSDMB	rs12453507	17:39896954
GP2, UMOD	rs12444268	16:20331250
RNLS	rs12416116	10:88275897
RPL32P23, RBM17	rs12251307	10:6081532
GSDMB, ZPBP2	rs12232497	17:39883866
STMND1	rs12203596	6:17120009
AC112204.3, IL7R	rs11954020	5:35883149
THADA	rs11888640	2:43579243
LINC00460, RPL35P9	rs11839053	13:106410694
BACH2	rs11755527	6:90248512
IRF1-AS1, AC116366.3	rs11741255	5:132475490
NKD1	rs117372389	16:50634166
PXK	rs11705721	3:58414687
C1orf141, IL23R	rs11580078	1:67203951
LINC01250	rs114846446	2:2944140
PLEKHA1	rs113306148	10:122400322
LINC02009, CCRL2	rs113010081	3:46415921
PRKCQ	rs11258747	10:6430929
UBASH3A	rs11203203	21:42416077

UBASH3A	rs11203202	21:42405248
ERBB3	rs11171739	12:56076841
EIF4A1P4, HIGD1AP1	rs11170445	12:53151908
CARD9	rs11145763	9:136369144
LINC02390, CLEC2D	rs11052552	12:9703362
FNBP1	rs10988542	9:129894985
ASCL2, MIR4686	rs10831551	11:2217058
AC024598.1, AC067751.1	rs10822050	10:62679011
RPL32P23, IL2RA	rs10795791	10:6066377
RNLS	rs10788599	10:88428167
HPSE2	rs10786436	10:98540425
GLIS3	rs10758593	9:4292083
MAPT	rs1052553	17:45996523
LINC02357	rs10517086	4:26083889
RNLS, AL353149.1	rs10509540	10:88263276
AC004830.2	rs10277986	7:50961290
TAP2, AL669918.1	rs1015166	6:32830954
IL25, EFS	rs10137082	14:23370824
AC132217.2, INS-IGF2	rs1004446	11:2148913