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Roles of environmental factors and microbiome in type 1 diabetes

Role faktorů prostředí a mikrobiomu u diabetu 1. typu

Bakalářská práce

Vedoucí práce:
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Poděkování

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Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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Podpis:

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ABSTRACT:

Type 1 diabetes mellitus (T1DM) is an insulin-dependent autoimmune disease. Its onset is characterized by an autoreactive self-destruction of β-cells within pancreatic islets. T1DM is influenced by multiple genetic predispositions, but since the incidence of the disease has increased dramatically in the past decades, especially in developed, western-type countries, the importance of the environmental factors has become obvious. There are various significant environmental influences that need to be addressed in the equation of variables. This bachelor thesis deals with the environmental variables and their mechanisms in T1DM and focuses on several areas of interest. It introduces frequently used spontaneous animal model of T1DM, pathogenetic mechanisms and T-cells in T1DM as well as regulatory immune cells and their mechanisms, in the light of hygiene and another hypothesis. Next it addresses the role of intestinal microbiota, dietary factors, mucosal immunity, their mechanisms and interactions in T1DM and extends to other, less researched, but important environmental variables such as circadian rhythm in connection with circadian gene expression depending on the rhythmicity of light/dark rotation and timing of food intake throughout the day, psychological/oxidative stress, and the effects of vitamin D deficiency or toxins present in water and the environment. The aim of the bachelor thesis is thus to introduce environmental factors, hygiene hypothesis, the NOD mouse model and to provide a comprehensive overview on environmental factors, some of them underestimated, and their mechanisms in prevention and pathogenesis of T1DM. Several of the environmental factors and their mechanisms, if better identified and understood, represent safe and promising strategies for secondary prevention or even at onset therapeutical interventions in T1DM.

KEY WORDS:

Type 1 diabetes, environmental factors, microbiome, bacteria, immune mechanisms, mucosal immunity, prevention, pathogenesis, NOD mice

ABSTRAKT:

Diabetes Mellitus 1 typu (T1DM) je insulin-dependentní autoimunní onemocnění, jehož iniciace je charakteristická autodestrukcí vlastních β-buněk, které jsou součástí ostrůvků pankreatu. T1DM je ovlivňována genetickou predispozicí, ale protože se v poslední dekádě ukazuje nárůst incidence tohoto onemocnění například v severských zemích Evropy, je zřejmé, že genetika nebude jedinou proměnnou a je třeba zohlednit nezanedbatelné vlivy vnějšího prostředí. Tato bakalářská práce pojednává o mechanismech vlivu vnějšího prostředí a zaměřuje se na několik oblastí poznání. Představuje často používaný spontánní zvířecí model T1DM, patogenetické mechanismy a T-buňky v souvislosti s T1DM, jakož i regulační imunitní buňky a jejich mechanismy, s ohledem na hygienu a další hypotézy. Dále se zabývá rolí střevní mikroflóry, dietními faktory, imunitou sliznic, mechanismy a interakcemi v T1DM a rozšiřuje se na další, méně prozkoumané, ale důležité proměnné prostředí, jako je cirkadiánní rytmus ve spojení s cirkadiánní genovou expresí v závislosti na rytmizaci světla/tmy a načasování příjmu potravy po celý den, psychologický/oxidační stres a účinky nedostatku vitaminu D nebo toxinů přítomných ve vodě a životním prostředí. Cílem bakalářské práce je tedy představit faktory prostředí, hygienické hypotézy, myší model NOD a poskytnout ucelený přehled faktorů prostředí a jejich mechanismů v prevenci a patogenezi T1DM. Několik faktorů prostředí a jejich mechanismů, pokud jsou lépe identifikovány a pochopeny, představují bezpečné a slibné strategie pro sekundární prevenci nebo dokonce v rámci terapeutických intervencí v rámci počátku rozvoje T1DM.

KLÍČOVÁ SLOVA:

Diabetes 1. typu, faktory vnějšího prostředí, mikrobiom, baktérie, imunitní mechanismy, slizniční imunita, prevence, patogeneze, NOD myši

CONTENT:

INTRODUCTION:

Type 1 Diabetes Mellitus (T1DM) is an insulin-dependent type of diabetes mellitus. It is a chronic autoimmune disease that becomes evident when insulin production is inadequate to control glucose metabolism. The autoimmune onset is well observable in non-obese diabetic (NOD) mice that spontaneously develop T1DM (Bach 1995). The disease is linked to several genetic predispositions, but its progression and onset are also influenced by epigenetic influences. Environmental factors and also the microbiome play an important role in the pathogenesis and even more recent increase of T1DM incidence worldwide (Patterson et al. 2019).

Environmental risk factors e.g. viruses are often considered as a trigger of β-cell destruction (Harrison 2005). The influence of the microbiome, mainly intestinal microbiome may be an important regulator and possibly a diseases-preventive factor within external influences on the development of T1DMs. Dietary factors are also known modifiers of the incidence of the disease. These factors may play a role in exposure throughout a lifespan to e.g., dairy or gluten. They may lead to or permit am increased rate of T1DM onset and its progression or, conversely, and perhaps even more likely, also to the disease prevention (Rewers a Ludvigsson 2016).

The integrity of the intestinal barrier is critical for keeping the proinflammatory contents of the intestine separate from the intestinal mucosa and the systemic circulation. (Visser et al. 2009) The immune system is tightly regulated by circadian rhythm and disrupted circadian rhythm can have devastating consequences associated with microbiome dysbiosis and T1DM progression (Cermakian et al. 2014) (see Figure 1).

Important factors include the composition (above all proteins) as well as quality of the diet in general the quality of drinking water and the presence of toxins in the diet (Benson et al. 2010), which can affect e.g. the permeability of the intestine (leaky gut syndrome) and the microbiome profiles (Wood Heickman et al. 2020). Microbiome imbalance may facilitate autoreactivity in genetically susceptible individuals (Paun et al. 2017).

Increased incidence of T1DM possibly reflects the delayed exposure and the decrease in overall infection frequency due to improved hygiene and overuse of antibiotics in industrialized countries in the last decades (Bach a Chatenoud 2012).

Among environmental factors in T1DM belongs, although somehow overshadowed also increased psychological stress. Chronic stress can activate the hypothalamic-pituitary-adrenal (HPA) axis and the nervous system. Both influence the immune cells and may increase insulin resistance (Sharif et al. 2018).

This bachelor thesis aims to introduce the environmental influences in the pathogenesis, progression, and prevention of type 1 diabetes mellitus. In addition, it also aims to briefly discuss possible mechanisms and interactions as well as their potential in prevention (primary or secondary) of T1DM.

1. Mechanisms of T1DM onset and immunoregulation

Type 1 Diabetes Mellitus (T1DM) is considered an autoimmune disease that is characterized by insulin deficiency resulting from the destruction of pancreatic β-cells. The pathogenesis of T1DM results from selective destruction of pancreatic β-cells by innate and adaptive immune systems (Hull et al. 2017).

T1DM is a T-cell-dependent immune-mediated disease. Insulin-producing pancreatic β-cells are invaded by a mononuclear infiltrate consisting of monocytes, macrophages, T-cells etc. and consequently destroyed (Kolb et al. 1995). CD4+ and CD8+ T-cells play a major role in the autoimmune process leading to the destruction of pancreatic β-cells (Yagi et al. 1992).

Self-directed immune reaction, in which the immune system recognizes β-cell specific antigens (e.g., proinsulin, GAD65, IA-2, IGPR etc.) (Han et al. 2013) , processes them as foreign, and reacts against them in a similar manner like to e.g. infectious agents results is the elimination of pancreatic β-cells and a decline in insulin secretion (Bach a Chatenoud 2001).

The causes of T1DM are very likely multifactorial and not exactly known although virus infections are believed to be responsible for the initial hit in genetically susceptible individuals. Both genetics but also environmental factors play important roles in T1DM. The genetic region which is strongly linked to T1DM is the human leukocyte antigen (HLA) locus (Steck a Rewers 2011). Risk genes for the development of T1DM are mostly genotyping HLA DR3, HLA DR4 (HLA DQ2, HLA DQ8) (Noble a Erlich 2012; She 1996). More than 50 risk genes have been so far identified in T1DM (Onengut-Gumuscu et al. 2015).

Environmental factors play major a role in the recent increase of T1DM incidence even though there much less information is available about their exact identities and mechanisms.

This is mainly due to the complexity of environmental factors, as it is difficult to isolate and study their specific mechanisms of impact (Knip a Simell 2012; Hamilton-Williams et al. 2021).

Environmental impact may be illustrated as an increase in the incidence of diabetes over a specific period in populations. In Finland, it has been reported that the incidence of the disease has increased 4,5 times from 1950 to the present. The incidence of T1DM has also increased in most post-communist countries due to an improvement in socio-economic levels. This fact is more likely to explain by changes in lifestyle and environment than by a change in genetic information (Onkamo et al. 1999).

It is generally suggested that T1DM is developing through elicitation of the immune system against β-cell antigens and initiation of proinflammatory responses. After antigen-presenting cells (APC) present β-cell antigens to the immune system, chronic effector autoimmune responses prevail also due to a dysbalanced or an inefficient regulation of the immune system, resulting in the destruction of β-cells (Wållberg a Cooke 2013).

1.1. Development of T-cells

The whole process begins in the thymus through the central tolerance of naive T-cells. Then clones, that would respond to the structures of the organism, are deleted. These mechanisms are not flawless. Autoreactive T-cells enter the peripheral system and together with other immune cells infiltrate the islets of the pancreas. An interesting fact is that the development of T1DM manifests itself symptomatically months or even years after a dysregulation (Kuhn et al. 2016; Marx et al. 2021).

1.1.1. Viruses

Viruses are believed by many to act as initial triggers of T1DM (Harrison 2005). Exact mechanisms are not exactly known. Viral respiratory infections in humans during the first year of life are associated with the onset and increased risk of T1DM (Beyerlein et al. 2013). Enteroviruses are one of the most discussed groups of viruses in connection with T1DM (Honkanen et al. 2017). Especially Coxsackie viruses (CV) are detected in the pancreas of patients with T1DM (Dotta et al. 2007) (see Figure 1).

Viral β-cell infections induce cellular stress, reduce insulin production, maintain the inflammatory environment in the pancreas, and increase MHC I expression on β-cells. This cascade leads to promotion of autoimmune disease (Richardson et al. 2016). Type B CV vaccines are tested in NOD mice model. It could serve as a primary protection for children before a development of T1DM (Hyöty et al. 2018).

1.2. Induction of diabetogenic T-cells

In the lymph nodes, antigens encounter naive T-cells. T-cells are activated and then migrate to the circulation and tissues, where they participate in humoral and cellular immunity. The pancreatic lymph node (PLN) is an important induction site in T1DM. PLN is a mucosal lymph node draining the pancreas and is thus entered by autoantigens from the islets. PLN is also the lymphoid organ critically important for induction of effector (but also regulatory) immune responses in T1DM (Höglund et al. 1999). The autoantigens get recognized by autoreactive T-cells giving rise to an anti-β-cell effector immunity (Gagnerault et al. 2002). T-cells are activated before entering the pancreas. The response in the pancreatic node then escalates (Jaakkola et al. 2003). T-cells involved in prediabetic insulitis express a specific homing marker for intestinal lymphoid tissue integrin α4β7 (Jaakkola et al. 2003). It confirms their association with the mucosal intestinal environment.

1.3. Effector T-cells in T1DM

CD8 and CD4 T-cells are necessary for the disease onset. The persistence of autoreactive memory (CD4, CD8) T-cells is a typical feature of T1DM (Burrack et al. 2017). The role of NK cells and innate immune mechanisms in the initial stages of β-cell elimination is also well documented (Gianchecchi et al. 2021). On the other hand, protective effects of NK cells were also reported (Beilke et al. 2012). Several studies reported the involvement of Th1 cells in pathogenesis of T1DM and it was originally considered a Th1 autoimmune disease (Burrack et al. 2017). However, later Th17 cells and also follicular CD4 T-cells have gained increasing attention in the pathogenesis of T1DM, also with respect to environmental factors (Shao et al. 2012; Walker a von Herrath 2016).

1.4. Diabetogenic T-cells

CD4 + T-cells are considered to be the essential and initial cell population that intervenes in T1DM (Delong et al. 2016). Nevertheless, when CD4+ T-cells are transferred alone to mice without a developed thymus, they induced insulitis only, but did not lead to β-cell destruction and hyperglycemia (Yagi et al. 1992). Insulitis or hyperglycemia occurs when CD8+ T-cells are transferred. Thus only co-administration of both populations induces insulitis with high CD8+ T-cell infiltration, hyperglycemia, and β-cell destruction (Yagi et al. 1992).

CD4+ T-cells are a key cell population that recognizes β-cell antigens and further releases several cytokines (IL-2, INF-γ). CD4+ T-cells are building up the inflammatory reaction which is leading to the activation of macrophages (M1) and cytotoxic CD8+ T-cells

(Angstetra et al. 2009). Altogether that induces β-cell apoptosis by Fas activation and perforin/granzyme release (Delong et al. 2016).

1.4.1. Autoantigens and neoepitopes

An amount of T1DM autoantigens have recently been identified - proinsulin, GAD65, IGRP, CHgA, IAPP, ZnT8, HSP GRP78, IA-2 and IA-2β. There is still not clear evidence about which antigens are initiating the onset of T1DM in humans (Roep a Peakman 2012). The detection of these antigens is caused by changes in the pancreas, either by internal damage to β-cells or by exogenous stimuli - e .g. a viral infection (Ilonen et al. 2019). Relatively recently it has been discovered that effector T-cells in T1DM recognize so-called neoepitopes in the periphery. Neoepitopes are products of aberrant translation of mRNA, post-translational modifications of self-peptides or protein fusions. These neoepitopes are generated under the influence of cellular stress e.g. high insulin demand or due to the environmental stressors (Mannering et al. 2019). There is for example the neoepitope which is the modification of the IA-2 antigen. This modification is caused by stress in the endoplasmic reticulum and leads to the formation of a complex that is recognized by CD4+ T-cells (Marre et al. 2018). The formation of neoepitopes explains why autoreactive T-cells escape both thymic deletion and mechanisms of peripheral tolerance. In addition, the neoepitopes also provide elegant explanation how the environment (stress, unspecific viruses) may participate in the initial phase of autoreactive CD4+ and consequently CD+8 T-cell responses.

1.5. Regulatory T-cells (Treg)

Mechanisms of disrupted immune homeostasis between the effector and regulatory arms of T-cell immune responses (also due to the changes in the environment) have been implicated in the recent increase of T1DM in genetically susceptible individuals (Sakaguchi et al. 2020; Gupta et al. 2014). In T1DM human intervention trials Foxp3 Tregs are frequently used as a biomarker together with monitoring of changes in T-cell effector subsets for assessing possible beneficial effects (Odegard et al. 2015). Several mechanisms are observed in patients with early-stage T1DM - depletion of CD4 and CD8 effector memory (Tem), depletion of central memory T-cells (Tcm) and shift in Teff / Treg ratio (Rigby et al. 2015).

1.6. FoxP3 + Tregs

FoxP3 + T cells are formed either in the thymus or at the periphery. If formation occurs in the thymus, they are referred to as tTreg. On the other hand, formation at the periphery leads to the formation of pTreg. Foxp3 Tregs are generated by action of IL-2 and TGF-β. They are

characterized by high expression of CD25 and intracellular FoxP3 (Bluestone a Tang 2005). Changes in Foxp3 Tregs have been repeatedly reported in the NOD mouse model of T1DM (Bluestone a Tang 2005) however other studies showed that the defect lies in the altered sensitivity of effector T-cells to regulatory mechanisms (D'Alise et al. 2008). Conflicting and inconclusive results came also from human trials of T1DM (Tan et al. 2014). However, a defect in the function of Foxp3 Tregs has been clearly documented in newly diagnosed children as well as autoantibody positive at-risk children (Vecchione et al. 2020). A meta-analysis study documented that in T1DM patients FoxP3+ Tregs produced lower levels of suppressive cytokine TGF-β but a decrease in IL-10 levels was not statistically significant (Qiao et al. 2016).

1.7. Regulatory type 1 (Tr1) T-cells

Regulatory type 1 (Tr1) T-cells are characterized by high IL-10 expression in comparison with the FoxP3+ Treg. They were first described by Groux et al. (Groux et al. 1997) and were characterized as FoxP3-negative, not CD25high CD4+ Tregs (Zeng et al. 2015), however as a result of the high expression of IL-10, Tr1 cells can transiently also express FoxP3 (Gregori et al. 2012), Tr1 cells (defined later as CD49b+LAG3+CD4+ T-cells) were shown as highly effective Tregs in T1DM. They prevented diabetes in the NOD-SCID model of diabetes transfer and Tr1 cells induced by a combination therapy even reverted diabetes in hyperglycemic NOD mice (Mbongue et al. 2019) (Yu et al. 2017).

1.8. Hygienic hypothesis

T1DM incidence is continuously increasing, especially in western type, developed countries (IDF Diabetes Atlas, 10th ed., Int. Diabetes Federation 2019). For example, it is substantially increasing in "clean" countries with higher level of hygiene such as Finland and is also occurring in younger and younger children ed countries (Patterson et al. 2009). In addition, it has been noted that children who had lower (home care) or delayed (firstborns) exposure to infection have a higher incidence of T1DM (Bach a Chatenoud 2012). It has been documented that the intestinal microbiota in children at T1DM onset is altered (Murri et al. 2013). In NOD mice model spontaneous T1DM incidence varies hugely depending on the quality of SPF conditions – the lowest is in "dirty" housing conditions (Pozzilli et al. 1993), on the other hand rederivation of the breeding nucleus renews higher T1DM development (Bach 2002). Germ-free NOD mice display high, 100% diabetes incidence and earlier diabetes onset compared to SPF litters (Wen et al. 2008).

In children, we can observe noticeable differences in microbiota colonization in connection with T1DM (Han et al. 2018). There is the evidence of decrease in Bifidobacterium and Lactobacillus, and vice versa increased Bacteroidetes with decreased Firmicutes (de Goffau et al. 2014). Although the above-mentioned phenomena are observed, the causal cause of the relationship between changes in the microbiome and the development of T1DM is not yet surely known. Thus the effect of microbiome changes, exposure to infections but also dietary factors may all contribute to the recent increase of T1DM incidence in developed countries (Craig et al. 2019). The real question is thus not so much about what is causing T1DM in genetically predisposed individuals, but rather what environmental factors were preventing T1DM in the past and are not so present anymore (Gale 2002).

2. The importance of NOD mouse model in T1DM

The Non-Obese Diabetic (NOD) mouse model (as well as the BioBreeding BB rats) is a very important tool to research pathogenesis, prevention and cure for T1DM. Unlike in many other animal models of autoimmune diseases, NOD mice develop T1DM spontaneously and the disease is not induced e.g., by immunization with an autoantigen or chemically induced. There are many similarities but also a few differences compared to human T1DM (Pearson et al. 2016). The NOD mouse origins form Japan, where Makino et al. observed, bred and reported spontaneously diabetic mice over 40 years ago (Makino et al. 1980). The NOD mice model is suitable for observing the role of both innate and adaptive cell subsets and mechanisms contributing to the disease development. The advantage of the NOD model is that T1DM is developing spontaneously, with incomplete penetrance of clinical onset of diabetes, and sensitive to environmental changes and manipulations i.e. corresponding to the recent increase of T1DM worldwide. This model allows to study natural course of development of type 1 (Pearson et al. 2016).

In addition to environmental triggers, similar and multiple predisposing genetic factors are paralleled in the NOD mouse model. There are over 50 genetic loci both in NOD mice and humans shown to be important in T1DM development and pathogenesis (Robertson a Rich 2018). They include genes related to immune system function and pancreatic β-cell functions (Noble a Erlich 2012). The major differences form the human T1DM comprise increase diabetes incidence in NOD females compared to males in SPF conditions, histological appearance of insulitis and the mononuclear infiltrate, that is massive in NOD mice compared

to humans, some differences in autoantibodies (no IA-2A auto-Abs in NOD mice) and increased resistance to ketoacidosis of the NOD mouse (Pearson et al. 2016).

2.1. Characteristics and advantages in NOD mice model

In NOD mice T1DM develops spontaneously and shares a similar genetic predisposition with human patients. NOD model also shares with human environmental factors which contribute to the onset of the disease. Pancreatic β-cells are destroyed by autoreactive T-cells. In animals kept in Specific Pathogen Free conditions with non-pathogenic microbiota present, NOD female's insulitis starts to occur at 5 - 6 weeks of age. Lower diabetes incidence and later development of insulitis is found in SPF NOD males. Lymphocytes and monocytes infiltrate in the peripheral parts of the islets. Peri-insulitis is followed by inflammation that permeates the entire islet, causing massive infiltration of immune system cells. In T1DM patients infiltration by immune cells is a lot smaller and scattered within the islets (In't Veld 2014). The difference between the human and NOD model is in the number of residual β-cells that are retained during T1DM. In humans, we find 20-30% of β-cells and in NOD mice 10-20% of β-cells (In't Veld 2014).

The incidence of T1DM depends on many factors - sex, mouse breeding, diets, and last but not least at all on microbiota composition, or quality of the SPF facilities. In SPF common SPF facilities screened only for pathogens according to the FELASA standards, a lower incidence is observed in SPF males (10-30%), while the incidence is higher in females NOD mice (60-80%). T1DM progresses often from age between 12 - 40 weeks of age (Wilberz et al. 1991) (Bach 2002). However commercial facilities that use a defined and limited bacterial mix for colonization of mice are reaching high, 100% diabetes incidence. This is similar to germ-free NOD mice. These models show a faster onset and higher incidence of T1DM - 100 % in female NOD mice (Wen et al. 2008; Bach 2002) On the other hand, NOD mice from conventional facilities display lower diabetes incidence, depending on the quality of the microbial environment and lengths of breeding (Pozzilli et al. 1993).

Environmental influences that affect the development of T1DM can be assessed, for example, by the degree of exposure infectious organisms (Cooke et al. 1999), exposure to gluten (Marietta et al. 2013) or wheat (Maurano et al. 2005). NOD mice are valuable also for studies on innate recognition of microbial components by e.g., TLR and NLR. These receptors interact with the gut microbiota and are important in modifying T1DM susceptibility (Wen et al. 2008).

The NOD model also contributes to the understanding of the microbiome-gut-PLN axis in T1DM, and the role of intestinal inflammation (Vaarala et al. 2008).

2.2. Development of new, humanized NOD mice strains

Humanized NOD mice have provided many discoveries into T1DM pathogenesis in humans (Gale a Gillespie 2001). Some NOD mice and human autoantigens are shared, while others differ in their epitopes. Therefore, it was difficult to translate research from the NOD mouse model to T1DM patients. Humanized NOD mice models bypass some of these disadvantages and have allowed researchers to discover mechanisms and cell populations that may develop into promising, novel and effective immunotherapies (Roep 2007). Humanized NOD mice are frequently used to identify and study class I and class II dependent β-cell autoreactive T cells and their clinical importance in T1DM (Tsui et al. 2008).

3. The role of Microbiota and environmental factors in T1DM

Genetic studies which are studying changes in the population's gene pool show that is changing. It has been reported that the HLA alleles of high risk for onset of T1DM decrease in the population and alleles of low risk concerning T1DM increase. This is one of the proofs for the role of environmental factors (Gillespie et al. 2004).

Besides genome, or environmental factors which are known as important players in the β-cell destruction. Microbiomes, mainly intestinal microbiome, seems to play an important role in the development of T1DM. There are multiple factors associated with the microbiome that may affect T1DM onset - breastfeeding, C-section, zonulin, dietary habits (gluten, dairy) (Norris et al. 1996), and other cumulative factors such as water quality, presence of toxins in the environment and diet, chronic stress and last but not least, and factors comprised by the Hygiene hypothesis. The cumulative character and interactions of the above-mentioned factors makes it difficult to identify exact environmental entities and their mechanisms. During the period of initiation and cumulative progression of environmental impacts, it is difficult to determine which ones are truly responsible for the development of the disease. The influence of lifestyle and mechanisms of mucosal (intestinal) immunity in connection with microbiome and its metabolites may affect progression to clinical onset T1DM in predisposed individuals (Paun et al. 2017). Increased incidence of T1DM probably reflects the decrease in overall infection frequency due to improved hygiene and antibiotics in industrialized countries (Bach a Chatenoud 2012). Another important player in T1DM is the chronic stress. Chronic stress

activates the hypothalamic-pituitary-adrenal (HPA) axis and the nervous system and it influences the immune cells as well as increases insulin resistance (Sharif et al. 2018).

3.1. The impact of the microbiome from an early age

The microbiome is defined as the many varied groups of microorganisms which are living in symbiosis with human. Microbial populations reach a community of around 4×10^{13} cells (Bäckhed et al. 2005). The colonization of digestive tract begins at birth and is fundamentally affected by the way of delivery. Vaginally delivered infants gain microbial communities strongly similar to maternal vaginal microbiota (mainly Lactobacillus). In the case of C-section, the intestines are colonized mostly by microorganisms similar to those which are found on the skin of the mother, (Staphylococcus, Clostridium genera) (Bäckhed et al. 2015). Thus, not surprisingly, Caesarean section is contributing to a remarkable 20% increased risk of T1DM (Cardwell et al. 2008).

3.2. Importance of microbiome symbiosis for humans

Symbiosis of humans with microorganisms is a very key ability that affects many important factors in our body - vitamin production, elimination of exogenous toxins, drug metabolism, support of cell proliferation and differentiation, maintaining the integrity of the intestinal barrier, maturation, and education of the immune system, neutrophil modulation, T-cell differentiation, or secretion of SCFAs. The human gut microbiota plays several important functions. It protects against pathogen overgrowth. It participates in the synthesis of important vitamins - B1, B2, B5, B6, B12, K, folic acid. It eliminates exogenous toxins and metabolizes specific drugs. Gut microbiota is also important for intestinal repair by promoting cellular proliferation and differentiation. This guarantees the important maintaining of the integrity of the gut barrier (Krishnan et al. 2015).

Microorganisms in the human gut play a crucial role in the maturation and education of the host immune system. The mucosal immune system has to discriminate between commensal and "danger" pathogenic bacteria. Pathogenic bacteria trigger a pro-inflammatory response whereas commensal bacteria have no such an effect or trigger anti-inflammatory responses (Goodman et al. 2011). Our microbiome modulates the migration and function of neutrophils and affects T-cell differentiation of regulatory T-cells (Tregs). Tregs are key mediators of immune tolerance (Paun et al. 2017). Another important mechanism by which the gut microbiota controls the immune system is through the secretion of short-chain fatty acids (SCFAs). SCFAs include molecules such as butyrate, acetate, and propionate. They are usually generated by the

fermentation of non-digestible carbohydrates (dietary fiber) (Ridaura et al. 2013) (see Figure 1).

SCFA secretion promotes G-protein-coupled receptors signaling pathways activation, inhibition of histone deacetylation, induction of metabolic changes by enhancing the activity of the mTOR complex in T-cells, which has a net effect on the inhibition of inflammatory cascades and the decrease of production of inflammatory cytokines (IL-10, IFN-γ) (Ridaura et al. 2013).

3.3. The connection between microbiota and T1DM

The connection between the microbiome, the immune system, and the development of T1DM can be observed from several angles – the connection with the mechanisms of non-specific and specific immunity. The connection between the gut microbiota and the pathogenesis, prevention, or onset of T1DM is being the subject of several studies in recent years. Microbiome effects on innate immunity is largely dependent on the Myd88 adaptor protein for several the TLRs. This adaptor molecule is involved in induction of innate immune responses by microbial patterns. If Myd88 is missing in the NOD mouse model, T1DM-related protection occurs. The protective effect of Myd88 deficiency is microbiota dependent. It confirms that interactions between the microbiome and innate immunity are important (Wen et al. 2008).

Another case in the demonstrable connection between T1DM, gut microbiota, and the adaptive immune system is represented by inflammatory lymphocytes, Th17 and type 3 innate lymphoid cells that are increased in the intestinal lamina propria of NOD mice, while tolerogenic dendritic cells and Treg are reduced in the lymph nodes draining the gut. These changes in adaptive immunity may have an impact on the activation of auto-reactive T-cells against β-cell antigens and T1DM development (Miranda et al. 2019).

The data on human microbiome changes in relation to T1DM are reviewed in Han et al (Han et al. 2018). Significantly decreased number of *Bifidobacterium* and *Lactobacillus*, and increased *Bacteroidetes* with decreased *Firmicutes* to *Bacteroidetes* ratio were reported in children with T1DM (Murri et al. 2013, s. 2). Whether these changes in microbiome profiles have a causative effect in T1DM is not known. Both *Bifidobacterium longum* and *Akkermansia muciniphila* with their e.g., production of SCFA have recently attracted a great deal of attention (Insel a Knip 2018; Y et al. 2018). Hänninen et al. (Hänninen et al. 2018) reported *Akkermansia muciniphila* having a beneficial metabolic and immune effects and it also reduced diabetes incidence when transferred to high incidence SPF NOD mice. In additions, study by

Yurkovetskiy et al. documented that gender difference in diabetes incidence of NOD mice is due to influences of gut microbiota (Yurkovetskiy et al. 2013). Further studies in gnotobiological models of germ-free and monoassociated NOD mice are necessary to uncover the role of selected bacteria in pathogenesis or prevention of T1DM.

4. Dietary risks in Diabetes Mellitus type I onset or progression

4.1. Gluten-free diet as a prevention of T1DM

Not carbohydrates but proteins were identified as the major pro-diabetic components within the non-purified animal diets to keep a high diabetes incidence in BB rats and NOD mice (Scott 1996; Coleman 1978). Conversely, hypoallergic baby diet based on hydrolyzed casein had a diabetes-preventive effect (Hoorfar et al. 1993). Later, a specifically designed non-purified, open-formula gluten-free diet (GFD) highly (from 64% to 15%) prevented diabetes in NOD mice that were exposed to it since in utero (Funda et al. 1999). Gluten intake directly affects the composition of the intestinal microflora. NOD mice fed a GFD have reduced numbers of caecal bacteria and Gram-positive bacteria in comparison with mice fed a standard diet containing wheat proteins (Hansen et al. 2006). Whether these changes have a causative role in the diabetes-preventive effect of GFD is not known.

Mothers who consumed large amounts of gluten during pregnancy give their offspring twice as likely chance to develop T1DM than mothers who ate during pregnancy gluten-free (Antvorskov et al. 2018). Higher gluten intake in early childhood may also be associated with a higher risk of T1DM (Lund-Blix et al. 2020). Encouraging is a case report of a 5-year-old boy diagnosed with T1DM and without celiac disease, who was on GFD diet in an attempt to preserve beta-cell functions and stayed without insulin therapy for 20 months (Sildorf et al. 2012). Recently, a 1-year intervention trial of GFD in newly diagnosed children with T1DM showed slower C-peptide decline, lower insulin demand and HbA1c and a more pronounced partial remission period in children on GFD (Neuman et al. 2020).

4.1.2. The effect of a GFD on immune cell populations

Gliadin fragments stimulate innate immune cells - such as macrophages or mast cells (Lavö et al. 1989; Tucková et al. 2002). Furthermore, GFD affects APC, the number of which decreases in mice in the mesenteric (MLN) and PLN nodes due to diet. Decreased expression of dendritic cell activation markers MHC-II, CD40 and CCR7 was also demonstrated in PLN, while the proportion of dendritic cells (DC) with tolerogenic properties increased (He et al.

2014). In contrast, when DCs are isolated from the bone marrow of BALB / c mice stimulated in vitro with wheat gluten, the expression of the activation markers MHC II, CD40, CD54 and CD86 and the secretion of chemokines is higher (Nikulina et al. 2004). It has been shown to reduce the proportion of IL-17 producing CD4+ T-cells (Antvorskov et al. 2012). In NOD mice on a gluten-free diet, only in utero, it reduces the infiltration of pancreatic islets by immune cells and reduces the expression of the transcription factor for Th17 RORγt in the gut (Antvorskov et al. 2016). A gluten-free diet reduces the number of proinflammatory Th1 lymphocytes in the MLN of BB rats and suppresses their production of IFN-γ (Chakir et al. 2005).

Furthermore, GFD administered since in utero reduces the proportion of IFN-γ + CD4+ CD3+ T cells and IL-22 + γδTCR + T cells in the spleen in mouse offspring (Haupt-Jorgensen et al. 2018). Changes in the number of regulatory FoxP3 + T-cells due to the GFD vary from study to study, but rather do not change (Antvorskov et al. 2012), but the cytokine profile of T-cells changes. The expression of pro-inflammatory cytokines (IL-2, IL-4, IL-17, IFN-γ) is reduced in mice on a gluten-free diet, while the expression of anti-inflammatory cytokines (IL-10, TGF-β) is increased. These changes are most pronounced in lymph nodes associated with the mucosa (MLN, PLN, PP) (Antvorskov et al. 2014). The proportion of γδ T cells, which are associated with T1D-associated mucosal tolerance and have a rather protective function, is increased in GF mice in all mucosal and systemic nodes examined in BALB / c mice (Antvorskov et al. 2012). In this work, a reduced proportion of CD8 + γδ T lymphocytes expressing the marker CD103, which targets these cells to the mucous membranes in PLN and MLN, was also found (Antvorskov et al. 2012). Thus, GFD promoted s regulatory cell subsets, especially within the intestinal, mucosal immune system and decreases pro-inflammatory s cytokine signatures.

4.1.3. The role of gluten and the association of celiac disease with T1DM

T1DM and celiac disease (CD) share a similar genetic background, with high susceptibility associated with the HLA-DQ2/DQ8 (Smyth et al. 2008). In addition, there is an increased association between CD and T1DM. The fact that most of these children develop T1DM first and not vice versa indirectly suggests a possible protective effect of GFD for progression from celiac disease to T1DM (Cosnes et al. 2008). Similarly, while it seems that the gut immune system is activated in T1DM patients, that activation is not only due to the shared genotype with CD patients, because intestinal inflammatory responses in T1DM patients are independent of a CD-associated genotype – HLA-DQ2 (Sánchez et al. 2011).

The onset and progression of the disease are often initiated when gluten peptides cross the intestinal epithelium. The peptides are supposed to be crosslinked or deamidated by the enzyme tissue transglutaminase (tTG). Deamidation leads to a negative charge in the gluten peptides. This mechanism is increasing their binding affinity to HLA-DQ2 or HLA-DQ8 on APCs, and also is increasing the chance of reaching the threshold necessary to prime gluten-reactive T-cells. The intestinal CD4+ T-cell response is directly leading against many different epitopes in the gluten proteins (Jabri a Sollid 2009).

The mechanism which is observed in this issue is that almost all T-cell lines from adult CD patients recognize the same 33mer gliadin peptide. It contains six HLA-DQ2-binding and T-cell-stimulatory epitopes and is resistant to intestinal digestion (Shan et al. 2002). CD is moreover characterized by IgA and IgG autoantibodies directed against tTG, by intestinal activation of T helper 17 cells, CD8+ T-cells, γδ T-cells, NK cells, DCs (Sollid 2000), and by the direct effect of gluten on intestinal enterocytes (Maiuri et al. 2003).

5. Another environmental influences of onset T1DM

5.1. Circadian rhythm

The circadian rhythm (CR) is an approximately 24 h pattern that alternates with almost all organisms (Hastings et al. 2003). It is a biological system that regulates the function of the organism on many levels - cellular, systemic, organ, behavior, vigilance / rest cycles etc (Mohawk et al. 2012). Vigilance and rest cycles drive physiological and cellular adaptations in a huge variety of processes such as gastrointestinal or metabolic processes and cellular transcription/translation (Reddy a O'Neill 2010). A certain correlation was found between circadian rhythm dysregulation and T1DM pathogenesis (Feng D. et al. 2012). Studies in NOD mice show that the dysregulation of the circadian rhythm can cause β-cell loss and onset of T1DM (Gale a Gillespie 2001).

The main role here is played by factors - CLOCK, ARNTL1, ARNTL2, CRY1, CRY2, PER1, PER2, PER3. Transcription and translation of clock components such as CLOCK, ARNTL1, ARNTL2, period circadian proteins (PER1, PER2, PER3) and cryptochromes (CRY1, CRY2) play an essential role in rhythm generation in the suprachiasmatic nucleus (SCN). SCN is the site of the circadian oscillator in mammals and the place of control of peripheral oscillations. There has already been shown direct relation of *CLOCK*-related genes in diabetes (Ko a Takahashi 2006).

Knockout mice for ARNTL1 and CLOCK exhibited a role for the β-cell clock in coordinating insulin secretion with the sleep/wake cycle. The elimination of the pancreatic clock can trigger the onset of T1DM (Marcheva et al. 2010). CRY is another part of the clock component and is necessary for the regulation of inflammatory cytokines through the NF-kappaB pathway (Narasimamurthy et al. 2012). Present data suggest a tight link between T1DM and the circadian rhythm through a variety of different gene pathways – including those that affect insulin metabolism and also immune regulation (Hofmann et al. 2013).

5.1.1. Circadian rhythm and ARNTL gene

The ARNTL2 gene is a key gene for association with T1DM that affects and controls IL-21 expression. IL-21 serves to control the proliferation of immune cells. The effects of the ARNTL2 gene have been demonstrated: downregulation in the NOD mouse model, control of the peripheral CD4 + T-cell proliferation, and association with the IL-21 gene promoter. The ARNTL2 gene has been discovered as a possible gene for T1DM within the IDD6 locus of the NOD mice model (Hung et al. 2006). The gene is downregulated in NOD mice compared to that of other NOD mouse strains. It has been shown many polymorphisms between these strains (Steward et al. 2013).

It was confirmed that ARNTL2 controls the proliferation of peripheral CD4+ T-cells and T1DM onset (He et al. 2010). It has also been shown that ARNTL2 binds to the promoter of the Il-21 gene, which controls the proliferation of immune cells itself (Spolski et al. 2008). Il-21 is located in T1DM locus IDD (McGuire et al. 2009). ARNTL2 probably controls Il-21expression without interaction with other circadian factors - CLOCK or BMAL (Lebailly et al. 2014). This fact points to a mechanism of controlling T1DM development independently of other known regulatory pathways.

5.1.2. Circadian rhythm and microbiome

Microorganisms colonize every accessible surface of the host organism – they are found on the skin, in nasal passages, and also in the gastrointestinal tract. Some bacteria also affect the circadian rhythm. Circadian rhythm and the molecular circadian clock are found in almost every cell with different molecular clocks regulated by different environmental cues (Yoo et al. 2004) (see Figure 1). Light/dark cycles are important for the regulation of the central circadian clock located in the SCN. The SCN has two majority functions. First, integrating inputs from the optic nerve, and second, synchronizing circadian rhythm in the periphery through parasympathetic and sympathetic signals (Welsh et al. 2010).

Light is a regulator of the central circadian rhythm. But there is another important marker of external cues that can regulate circadian clocks in peripheral tissues. Peripheral tissues are regulated by nutrient availability and have an impact on circadian clocks in the intestine and liver. We can regulate it by the timing of food availability throughout the day (Mattson et al. 2014). Another factor of regulating circadian rhythm is also physical activity (Youngstedt et al. 2016).

Dysregulation of circadian rhythm in the human organism is very usual due to lifestyle and can be the consequence of various factors – shift work and jet lag are being some of the most obvious causes. Chronic diseases are usually associated with circadian rhythm dysregulation due to the promotion of inflammatory processes (Clemente et al. 2012). Here are several factors that can influence significant proinflammatory changes in the organism. It can lead to dysfunction of intestinal barrier integrity (Caricilli et al. 2014). The changes in the microbiota are defined by an increase in pro-inflammatory bacteria and a decrease in anti-inflammatory butyrate-producing bacteria (Voigt et al. 2014).

The integrity of the intestinal barrier is crucial for keeping the proinflammatory parts of the intestine separate from the intestinal mucosa and the systemic circulation(Farhadi et al. 2003). Intestinal dysbiosis can have proinflammatory consequences in the intestinal mucosa and these factors can transform immune function. The immune system is tightly regulated by circadian rhythm and its dysregulation can be devastating (Cermakian et al. 2014). Circadian disruption by night shifts usually leads to increased intestinal Th17 cells (Yu et al. 2013).

5.2. Psychological stress

The β-cell stress hypothesis suggests that any exogenous/endogenous factor that induces insulin resistance, which leads to extra pressure on the β-cells, should be categorized as a risk factor for T1DM (see Figure 1). In case of psychological stress occurs to insulin sensitivity decrease and insulin resistance increase. This phenomenon may be an important factor in the development/onset of T1DM. An increase in adrenaline or testosterone increases the need for insulin because the organism is preparing for a fight/flight reaction. Human physiology in this case leads to an increase in cortisol concentration and also to a reduction of insulin sensitivity. These belongings lead to amplified demand for the insulin-producing β-cells. Elevated pressure on the β-cells leads to increased presentation of autoantigens (Kampe et al. 1989). High concentrations of diabetes-related autoantibodies trigger autoimmune destruction of β-cells. For this phenomenon to occur, these possibilities must be met - genetic disposition for

autoimmunity, a deficient immune balance, or an immature or under-engaged immune defense (Kolb a Elliott 1994).

5.2.1 Link between T1DM and psychological stress

Psychological stress may play an important role in the development of diabetes. Both types of DM (T1DM, T2DM) result from the loss of β-cell function in association with insulin resistance (Wilkin 2001). Insulin resistance was found as the primary accelerator for T1DM (also T2DM) (Wilkin 2001) and is also expected to increase β-cell stress and amplification of an autoimmune response in organisms who have the genetic predisposition (Kibirige et al. 2003). The β-cell stress hypothesis suggests that any phenomenon that induces insulin resistance and thereby adds extra pressure on the β-cells should be regarded as a risk factor for diabetes (Ludvigsson 2006).

5.2.2. Oxidative stress in relationship with T1DM

Oxidative stress has been closely associated with inflammatory conditions including T1DM. T-cell-mediated infiltration has been shown to increase the release of ROS and proinflammatory cytokines, which lead to destruction (Haskins et al. 2003). The other important aspect which leads to inflammation is the clearance of apoptotic cells. It should prevent cell lysis and as a consequence to prevent the release of proinflammatory content that fuels inflammatory pathways (Savill 1997). Several lines of evidence highlight the role of oxidative stress on T1DM. The presumed mechanisms involve changes at the hypothalamic-pituitary-adrenal axis, the influence of the nervous system on immune cells, and also insulin resistance. The modification of the hypothalamic-pituitary-adrenal (HPA) axis and changes in hormonal levels (glucocorticoids), play a key role in the response of organisms to stress. Catecholamines released from the adrenal medulla also affect the stress response (Geer et al. 2014).

The excessive counterregulatory molecules support insulin resistance, which plays an important role in T1DM development/progression (Kirsch et al. 1983). The binding of catecholamines on monocytes leads to increase production of proinflammatory cytokines (IL-1á) (Grisanti et al. 2010). Relating to APC, the binding of norepinephrine results in decreased production of IL-12, a driver for Th1 production (Tsatsoulis 2006). The activation of adrenergic receptors on Th1 cells inhibits the secretion of IFN-γ. IFN-γ is an important regulator of Th1 development. Stress has been also shown to result in elevated Th2 cytokines including IL-4, IL-10, IL-13 (Ramírez et al. 1996). These factors indicate that stress disfigures the Th1/Th2 balance toward a Th2-dominant immunity (Iwakabe et al. 1998).

5.3. Vitamin D

The most well-known function of vitamin D is its role in calcium homeostasis and bone metabolism (Munger et al. 2006). Epidemiologic evidence supports the potential role of vitamin D in the pathogenesis of T1DM. The vitamin D receptor (VDR) may play a role in T1DM pathogenesis/onset or regulation. VDR has been found in almost every tissue in the human organism, including the cells of the immune system (Pani et al. 2000). The VDR gene is located on chromosome 12 (Busta et al. 2011). Some allelic variations of the VDR gene have been associated with an increased risk for T1DM (Chang et al. 2000). Vitamin D possibly may suppress the expression of MHCII complex antigens and the production of cytokines. It may support the induction of Treg. Together, these immunomodulatory effects of vitamin D (see Figure 1) may protect the β-cells of the pancreas (Busta et al. 2011).

The active form of vitamin D is involved in the pathogenesis of T1DM through the regulation of genes encoding proteins associated with glucose metabolism and normal immune system function. 25-hydroxyvitamin D is also important for the regulation of insulin secretion by β-cells and in the sensitivity of tissues to insulin. The Ca-binding protein (calbindin) transports proteins in the kidneys and the small intestine. These proteins are dependent on the function of vitamin D and allow the absorption of calcium from the intestine and renal tubules into the body. Calbindin protects β-cells from apoptosis. This means that vitamin D affects the function of T-cells and APC. This interferes with several autoimmune processes in β-cells and may prevent the onset of T1DM (Ysmail-Dahlouk et al. 2016).

Discussion and conclusion

T1DM is an insulin-dependent autoimmune disease that is the result of an interaction of genetic and environmental factors. The initial trigger - likely a virus (Harrison 2005) and the very early stages of the pathogenic process are not yet clearly identified and fully understood. There is a great deal of information on the role of pathogenic effector T-cells in the disease development as well as potential of regulatory immune mechanisms in disease prevention or even reversal (Harrison 2005, Walker a von Herrath 2016, (Wållberg a Cooke 2013) Recently, the described T-cell neoantigens and neoepitopes attract significant attention as they also proved explanation for the influence of environmental stressors in generation of beta cell specific autoreactive T-cell responses. Although the role of Foxp3 Tregs in T1DM was extensively addressed, they brought sometime conflicting or inconclusive data on their physiological role in T1DM, especially in humans (Tan et al. 2014; Qiao et al. 2016). The

relatively newly described peripheral-induced Tr1 cells are gaining more interest also in T1DM (Mbongue et al. 2019).

The interactions and more frequently protective than pathogenic role of environmental factor has been postulated in the hygiene hypothesis and still reflects the fact that T1DM is on a steady rise in the developed, "clean" countries (Patterson et al. 2009). Supportive data are coming also form the animal models (Pozzilli et al. 1993). For decades, the environmentally sensitive NOD mouse model, that spontaneously develops T1DM has been a very valuable tool for conducting research in the genetic susceptibility, the mechanism of disease development and pathogenesis or prevention under environmental influences (Pearson et al. 2016). NOD humanized mouse models are widely used in translational research and to study autoreactive T-cells (Roep 2007). In NOD mice intestinal microbiota has a disease preventive effect, while germ-free animals display 100% and rapid onset T1DM (Wen et al. 2008). Several microbiome changes have been described in children with T1DM, also in relation to dietary interventions, but more, preferentially gnotobiotic animal studies are required to clarify the robustness and mechanism of such prevention as well interactions with diets. Changes in the intestinal microflora in early childhood have an impact on the development of T1DM, mainly due to immunoregulation, e.g., the method of delivery. Whether it is vaginal or C-section (Cardwell et al. 2008) or vitamin D deficiency of mother (Ysmail-Dahlouk et al. 2016).

In early childhood, breastfeeding is another factor that can affect the colonization of a microbiome by symbiotic/dysbiotic ratio bacteria (Bäckhed et al. 2015), exposure to a sterile environment (Han et al. 2018) or antibiotics. Microorganisms inhabiting the intestinal mucosa can also be influenced by dietary habits and possible supplementation of probiotics of commensal strains of individual microbiota (Mishra et al. 2019).

Recent studies have pointed to the phenomenon of the intestinal microbiome, its metabolites and diurnal rhythmicity, which depend on the alternation of light / dark as well as the timing of food intake during the day. Circadian rhythm and its oscillation can be disrupted due to jet lag, poor eating habits and sleep rhythm (Ko a Takahashi 2006). Gut microbial metabolites influence central and hepatic clock gene expression and sleep duration and regulate body composition through circadian transcription factors (Cermakian et al. 2014). It has been discovered that ARNTL2 controls the expression of the IL-21 gene and that high levels of ARNTL2 suppress IL-21 expression. It connects well with the role of IL-21 in the immune system, the expansion of T-cells, and in particular as being a major factor in T1DM (He et al.

2010). These findings reinforce the evidence that components of the immune system undergo circadian rhythm control (Scheiermann et al. 2013).

Among other environmental influences, it is important to mention the connection between T1DM and psychological/oxidative stress. Psychological stress, throughout β-cell stress or direct influence on the immune system. However, further empirical data are needed to support this hypothesis (Sharif et al. 2018). Oxidative stress probably contributes to promotion of the initiation and progression of T1DM. The β-cell stress hypothesis suggests that any phenomenon that induces insulin resistance and thereby adds extra pressure on the highly metabolically active β-cells should be regarded as a risk factor for diabetes (Ludvigsson2006). Enterovirus infections are a widespread factor that promotes the autoimmune response in β-cell destruction in genetically predisposed individuals. Viral infections act as accelerators of autoimmune processes. Nevertheless, they remain as just one factor in the complexity of T1DM (Richardson et al. 2016). Enterovirus vaccines could be potential game changers in the primary prevention of T1DM (Hyöty et al. 2018).

Vitamin D deficiency plays a role in increasing the chance of initiating T1DM (Ysmail-Dahlouk et al. 2016). From a therapeutic point of view, vitamin D may potentially be suggested as an immunological adjuvant and a potential anti-inflammatory agent in individuals at risk of T1DM (Ysmail-Dahlouk et al. 2016). Data on vitamin D supplementation in connection with decreased β-cell function in T1DM remain inconclusive. Specific subpopulations could be advised to increase the dose of vitamin D to achieve the required serum concentration of 25(OH)D for the prevention or treatment of T1DM (Ko a Takahashi 2006).

Taking into account the above-mentioned environmental phenomena, which play a significant role in influencing the propagation and progression of T1DM in genetically predispositions of individuals, it is clear that the T1DM can be subjected to a number of preventive steps and changes in the future, especially as screening for at-high risk individuals is becomes more available. Changes in the lifestyle and/or virus vaccines should be able to promote so far untouched primary prevention in T1DM, whereas more gnotobiotic animal studies are required to address the complexity of microbiome, dietary as well as other (circadian rhythm, stress, vitamin D) environmental factors and their impact on mucosal immunity. Environmental factors and their mechanisms should serve as a basis for prospective clinical trials as they represent rather safe and not yet fully explored means for secondary prevention or even interventions in at-risk or recent onset T1DM individuals.

REFERENCES:

ANGSTETRA, Eveline, Kate L. GRAHAM, Sarah EMMETT, Nadine L. DUDEK, Rima DARWICHE, Rochelle AYALA-PEREZ, Janette ALLISON, Pere SANTAMARIA, Thomas W. H. KAY a Helen E. THOMAS, 2009. In vivo effects of cytokines on pancreatic beta-cells in models of type I diabetes dependent on CD4(+) T lymphocytes. *Immunology and Cell Biology* [online]. **87**(2), 178–185. ISSN 0818-9641. Dostupné z: doi:10.1038/icb.2008.81

ANTVORSKOV, Julie C., Thorhallur I. HALLDORSSON, Knud JOSEFSEN, Jannet SVENSSON, Charlotta GRANSTRÖM, Bart O. ROEP, Trine H. OLESEN, Laufey HROLFSDOTTIR, Karsten BUSCHARD a Sjudur F. OLSEN, 2018. Association between maternal gluten intake and type 1 diabetes in offspring: national prospective cohort study in Denmark. *BMJ (Clinical research ed.)* [online]. **362**, k3547. ISSN 1756-1833. Dostupné z: doi:10.1136/bmj.k3547

ANTVORSKOV, Julie C., Knud JOSEFSEN, Kåre ENGKILDE, David P. FUNDA a Karsten BUSCHARD, 2014. Dietary gluten and the development of type 1 diabetes. *Diabetologia* [online]. **57**(9), 1770–1780. ISSN 1432-0428. Dostupné z: doi:10.1007/s00125-014-3265-1

ANTVORSKOV, Julie C., Knud JOSEFSEN, Martin HAUPT-JORGENSEN, Petra FUNDOVA, David P. FUNDA a Karsten BUSCHARD, 2016. Gluten-Free Diet Only during Pregnancy Efficiently Prevents Diabetes in NOD Mouse Offspring. *Journal of Diabetes Research* [online]. **2016** [vid. 2021-05-01]. ISSN 2314-6745. Dostupné z: doi:10.1155/2016/3047574

ANTVORSKOV, Julie Christine, Petra FUNDOVA, Karsten BUSCHARD a David P. FUNDA, 2012. Impact of dietary gluten on regulatory T cells and Th17 cells in BALB/c mice. *PloS One* [online]. **7**(3), e33315. ISSN 1932-6203. Dostupné z: doi:10.1371/journal.pone.0033315

BÄCKHED, Fredrik, Ruth E. LEY, Justin L. SONNENBURG, Daniel A. PETERSON a Jeffrey I. GORDON, 2005. Host-bacterial mutualism in the human intestine. *Science (New York, N.Y.)* [online]. **307**(5717), 1915–1920. ISSN 1095-9203. Dostupné z: doi:10.1126/science.1104816

BÄCKHED, Fredrik, Josefine ROSWALL, Yangqing PENG, Qiang FENG, Huijue JIA, Petia KOVATCHEVA-DATCHARY, Yin LI, Yan XIA, Hailiang XIE, Huanzi ZHONG, Muhammad Tanweer KHAN, Jianfeng ZHANG, Junhua LI, Liang XIAO, Jumana AL-AAMA, Dongya ZHANG, Ying Shiuan LEE, Dorota KOTOWSKA, Camilla COLDING, Valentina TREMAROLI, Ye YIN, Stefan BERGMAN, Xun XU, Lise MADSEN, Karsten KRISTIANSEN, Jovanna DAHLGREN, Jun WANG a Wang JUN, 2015. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. *Cell Host & Microbe* [online]. **17**(5), 690–703. ISSN 1934-6069. Dostupné z: doi:10.1016/j.chom.2015.04.004

BACH, J. F., 1995. Insulin-dependent diabetes mellitus as a beta-cell targeted disease of immunoregulation. *Journal of Autoimmunity* [online]. **8**(4), 439–463. ISSN 0896-8411. Dostupné z: doi:10.1016/0896-8411(95)90001-2

BACH, J. F. a L. CHATENOUD, 2001. Tolerance to islet autoantigens in type 1 diabetes. *Annual Review of Immunology* [online]. **19**, 131–161. ISSN 0732-0582. Dostupné z: doi:10.1146/annurev.immunol.19.1.131

BACH, Jean-Francois, 2002. The effect of infections on susceptibility to autoimmune and allergic diseases. *The New England Journal of Medicine* [online]. **347**(12), 911–920. ISSN 1533-4406. Dostupné z: doi:10.1056/NEJMra020100

BACH, Jean-François a Lucienne CHATENOUD, 2012. The Hygiene Hypothesis: An Explanation for the Increased Frequency of Insulin-Dependent Diabetes. *Cold Spring Harbor Perspectives in Medicine* [online]. **2**(2) [vid. 2021-05-01]. ISSN 2157-1422. Dostupné z: doi:10.1101/cshperspect.a007799

BEILKE, Joshua N., Craig T. MEAGHER, Karoline HOSIAWA, Marine CHAMPSAUR, Jeffrey A. BLUESTONE a Lewis L. LANIER, 2012. NK cells are not required for spontaneous

autoimmune diabetes in NOD mice. *PloS One* [online]. **7**(4), e36011. ISSN 1932-6203. Dostupné z: doi:10.1371/journal.pone.0036011
BENSON, Victoria S., John A. VANLEEUWEN, Jennifer TAYLOR, George S. SOMERS, Patricia A. MCKINNEY a Linda VAN TIL, 2010. Type 1 diabetes mellitus and components in drinking water and diet: a population-based, case-control study in Prince Edward Island, Canada. *Journal of the American College of Nutrition* [online]. **29**(6), 612–624. ISSN 1541-1087. Dostupné z: doi:10.1080/07315724.2010.10719900
BEYERLEIN, Andreas, Fabienne WEHWECK, Anette-Gabriele ZIEGLER a Maren PFLUEGER, 2013. Respiratory Infections in Early Life and the Development of Islet Autoimmunity in Children at Increased Type 1 Diabetes Risk: Evidence From the BABYDIET Study. *JAMA Pediatrics* [online]. **167**(9), 800–807. ISSN 2168-6203. Dostupné z: doi:10.1001/jamapediatrics.2013.158
BLUESTONE, Jeffrey A. a Qizhi TANG, 2005. How do CD4+CD25+ regulatory T cells control autoimmunity? *Current Opinion in Immunology* [online]. **17**(6), 638–642. ISSN 0952-7915. Dostupné z: doi:10.1016/j.coi.2005.09.002
BURRACK, Adam L., Tijana MARTINOV a Brian T. FIFE, 2017. T Cell-Mediated Beta Cell Destruction: Autoimmunity and Alloimmunity in the Context of Type 1 Diabetes. *Frontiers in Endocrinology* [online]. **8**, 343. ISSN 1664-2392. Dostupné z: doi:10.3389/fendo.2017.00343
BUSTA, Agustin, Bianca ALFONSO a Leonid PORETSKY, 2011. *Role of Vitamin D in the Pathogenesis and Therapy of Type 1 Diabetes Mellitus* [online]. B.m.: IntechOpen [vid. 2021-05-01]. ISBN 978-953-307-756-7. Dostupné z: doi:10.5772/21918
CARDWELL, C. R., L. C. STENE, G. JONER, O. CINEK, J. SVENSSON, M. J. GOLDACRE, R. C. PARSLOW, P. POZZILLI, G. BRIGIS, D. STOYANOV, B. URBONAITE, S. SIPETIĆ, E. SCHOBER, C. IONESCU-TIRGOVISTE, G. DEVOTI, C. E. DE BEAUFORT, K. BUSCHARD a C. C. PATTERSON, 2008. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia* [online]. **51**(5), 726–735. ISSN 0012-186X. Dostupné z: doi:10.1007/s00125-008-0941-z
CARICILLI, Andrea Moro, Angela CASTOLDI a Niels Olsen Saraiva CÂMARA, 2014. Intestinal barrier: A gentlemen's agreement between microbiota and immunity. *World Journal of Gastrointestinal Pathophysiology* [online]. **5**(1), 18–32. ISSN 2150-5330. Dostupné z: doi:10.4291/wjgp.v5.i1.18
CERMAKIAN, Nicolas, Susan WESTFALL a Silke KIESSLING, 2014. Circadian clocks and inflammation: reciprocal regulation and shared mediators. *Archivum Immunologiae Et Therapiae Experimentalis* [online]. **62**(4), 303–318. ISSN 1661-4917. Dostupné z: doi:10.1007/s00005-014-0286-x
CLEMENTE, Jose C., Luke K. URSELL, Laura Wegener PARFREY a Rob KNIGHT, 2012. The impact of the gut microbiota on human health: an integrative view. *Cell* [online]. **148**(6), 1258–1270. ISSN 1097-4172. Dostupné z: doi:10.1016/j.cell.2012.01.035
COLEMAN, D. L., 1978. Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. *Diabetologia* [online]. **14**(3), 141–148. ISSN 0012-186X. Dostupné z: doi:10.1007/BF00429772
COOKE, A., P. TONKS, F. M. JONES, H. O'SHEA, P. HUTCHINGS, A. J. FULFORD a D. W. DUNNE, 1999. Infection with Schistosoma mansoni prevents insulin dependent diabetes mellitus in non-obese diabetic mice. *Parasite Immunology* [online]. **21**(4), 169–176. ISSN 0141-9838. Dostupné z: doi:10.1046/j.1365-3024.1999.00213.x
COSNES, Jacques, Christophe CELLIER, Sheila VIOLA, Jean-Frederic COLOMBEL, Laurent MICHAUD, Jacques SARLES, Jean-Pierre HUGOT, Jean-Louis GINIES, Alain DABADIE, Olivier MOUTERDE, Matthieu ALLEZ, Isabelle NION-LARMURIER, a GROUPE D'ETUDE ET DE RECHERCHE SUR LA MALADIE COELIAQUE, 2008.

Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association* [online]. **6**(7), 753–758. ISSN 1542-7714. Dostupné z: doi:10.1016/j.cgh.2007.12.022
CRAIG, Maria E., Ki Wook KIM, Sonia R. ISAACS, Megan A. PENNO, Emma E. HAMILTON-WILLIAMS, Jennifer J. COUPER a William D. RAWLINSON, 2019. Early-life factors contributing to type 1 diabetes. *Diabetologia* [online]. **62**(10), 1823–1834. ISSN 1432-0428. Dostupné z: doi:10.1007/s00125-019-4942-x
D'ALISE, Anna Morena, Vincent AUYEUNG, Markus FEUERER, Junko NISHIO, Jason FONTENOT, Christophe BENOIST a Diane MATHIS, 2008. The defect in T-cell regulation in NOD mice is an effect on the T-cell effectors. *Proceedings of the National Academy of Sciences of the United States of America* [online]. **105**(50), 19857–19862. ISSN 1091-6490. Dostupné z: doi:10.1073/pnas.0810713105
DE GOFFAU, Marcus C., Susana FUENTES, Bartholomeus VAN DEN BOGERT, Hanna HONKANEN, Willem M. DE VOS, Gjalt W. WELLING, Heikki HYÖTY a Hermie J. M. HARMSEN, 2014. Aberrant gut microbiota composition at the onset of type 1 diabetes in young children. *Diabetologia* [online]. **57**(8), 1569–1577. ISSN 1432-0428. Dostupné z: doi:10.1007/s00125-014-3274-0
DELONG, Thomas, Timothy A. WILES, Rocky L. BAKER, Brenda BRADLEY, Gene BARBOUR, Richard REISDORPH, Michael ARMSTRONG, Roger L. POWELL, Nichole REISDORPH, Nitesh KUMAR, Colleen M. ELSO, Megan DENICOLA, Rita BOTTINO, Alvin C. POWERS, David M. HARLAN, Sally C. KENT, Stuart I. MANNERING a Kathryn HASKINS, 2016. Pathogenic CD4 T cells in type 1 diabetes recognize epitopes formed by peptide fusion. *Science (New York, N.Y.)* [online]. **351**(6274), 711–714. ISSN 1095-9203. Dostupné z: doi:10.1126/science.aad2791
DOTTA, Francesco, Stefano CENSINI, Astrid G. S. VAN HALTEREN, Lorella MARSELLI, Matilde MASINI, Sabrina DIONISI, Franco MOSCA, Ugo BOGGI, Andrea Onetti MUDA, Stefano Del PRATO, John F. ELLIOTT, Antonello COVACCI, Rino RAPPUOLI, Bart O. ROEP a Piero MARCHETTI, 2007. Coxsackie B4 virus infection of β cells and natural killer cell insulitis in recent-onset type 1 diabetic patients. *Proceedings of the National Academy of Sciences of the United States of America* [online]. **104**(12), 5115–5120. ISSN 0027-8424. Dostupné z: doi:10.1073/pnas.0700442104
FARHADI, Ashkan, Ali BANAN, Jeremy FIELDS a Ali KESHAVARZIAN, 2003. Intestinal barrier: an interface between health and disease. *Journal of Gastroenterology and Hepatology* [online]. **18**(5), 479–497. ISSN 0815-9319. Dostupné z: doi:10.1046/j.1440-1746.2003.03032.x
FUNDA, David P, Anne KAAS, Troels BOCK, Helena TLASKALOVAÂ-HOGENOVAÂ a Karsten BUSCHARD, 1999. Gluten-free diet prevents diabetes in NOD mice. *Diabetes Metab Res Rev*. 5.
GAGNERAULT, Marie-Claude, Jian Jian LUAN, Chantal LOTTON a Françoise LEPAULT, 2002. Pancreatic lymph nodes are required for priming of beta cell reactive T cells in NOD mice. *The Journal of Experimental Medicine* [online]. **196**(3), 369–377. ISSN 0022-1007. Dostupné z: doi:10.1084/jem.20011353
GALE, E. A. a K. M. GILLESPIE, 2001. Diabetes and gender. *Diabetologia* [online]. **44**(1), 3–15. ISSN 0012-186X. Dostupné z: doi:10.1007/s001250051573
GALE, Edwin A. M., 2002. The rise of childhood type 1 diabetes in the 20th century. *Diabetes* [online]. **51**(12), 3353–3361. ISSN 0012-1797. Dostupné z: doi:10.2337/diabetes.51.12.3353
GEER, Eliza B., Julie ISLAM a Christoph BUETTNER, 2014. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism. *Endocrinology and Metabolism Clinics of North America* [online]. **43**(1), 75–102. ISSN 1558-

4410. Dostupné z: doi:10.1016/j.ecl.2013.10.005
GIANCHECCHI, Elena, Domenico V. DELFINO a Alessandra FIERABRACCI, 2021. Natural Killer Cells: Potential Biomarkers and Therapeutic Target in Autoimmune Diseases? *Frontiers in Immunology* [online]. **12**, 616853. ISSN 1664-3224. Dostupné z: doi:10.3389/fimmu.2021.616853
GILLESPIE, Kathleen M., Steven C. BAIN, Anthony H. BARNETT, Polly J. BINGLEY, Michael R. CHRISTIE, Geoffrey V. GILL a Edwin A. M. GALE, 2004. The rising incidence of childhood type 1 diabetes and reduced contribution of high-risk HLA haplotypes. *Lancet (London, England)* [online]. **364**(9446), 1699–1700. ISSN 1474-547X. Dostupné z: doi:10.1016/S0140-6736(04)17357-1
GOODMAN, Andrew L., George KALLSTROM, Jeremiah J. FAITH, Alejandro REYES, Aimee MOORE, Gautam DANTAS a Jeffrey I. GORDON, 2011. Extensive personal human gut microbiota culture collections characterized and manipulated in gnotobiotic mice. *Proceedings of the National Academy of Sciences of the United States of America* [online]. **108**(15), 6252–6257. ISSN 1091-6490. Dostupné z: doi:10.1073/pnas.1102938108
GREGORI, Silvia, Rosa BACCHETTA, Manuela BATTAGLIA a Maria Grazia RONCAROLO, 2012. Type 1 regulatory T (Tr1) cells: from the bench to the bedside. *Journal of Translational Medicine* [online]. **10**(Suppl 3), I7. ISSN 1479-5876. Dostupné z: doi:10.1186/1479-5876-10-S3-I7
GRISANTI, Laurel A., Janel EVANSON, Erica MARCHUS, Heather JORISSEN, Andrew P. WOSTER, Wanda DEKREY, Edward R. SAUTER, Colin K. COMBS a James E. PORTER, 2010. Pro-inflammatory responses in human monocytes are beta1-adrenergic receptor subtype dependent. *Molecular Immunology* [online]. **47**(6), 1244–1254. ISSN 1872-9142. Dostupné z: doi:10.1016/j.molimm.2009.12.013
GROUX, H., A. O'GARRA, M. BIGLER, M. ROULEAU, S. ANTONENKO, J. E. DE VRIES a M. G. RONCAROLO, 1997. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* [online]. **389**(6652), 737–742. ISSN 0028-0836. Dostupné z: doi:10.1038/39614
GUPTA, Shipra, Karen CEROSALETTI a S. Alice LONG, 2014. Renegade homeostatic cytokine responses in T1D: drivers of regulatory/effector T cell imbalance. *Clinical Immunology (Orlando, Fla.)* [online]. **151**(2), 146–154. ISSN 1521-7035. Dostupné z: doi:10.1016/j.clim.2014.02.007
HAMILTON-WILLIAMS, Emma E., Graciela L. LORCA, Jill M. NORRIS a Jessica L. DUNNE, 2021. A Triple Threat? The Role of Diet, Nutrition, and the Microbiota in T1D Pathogenesis. *Frontiers in Nutrition* [online]. **8**, 600756. ISSN 2296-861X. Dostupné z: doi:10.3389/fnut.2021.600756
HAN, Hui, Yuying LI, Jun FANG, Gang LIU, Jie YIN, Tiejun LI a Yulong YIN, 2018. Gut Microbiota and Type 1 Diabetes. *International Journal of Molecular Sciences* [online]. **19**(4). ISSN 1422-0067. Dostupné z: doi:10.3390/ijms19040995
HAN, Shuhong, William DONELAN, Hai WANG, Westley REEVES a Li-Jun YANG, 2013. Novel autoantigens in type 1 diabetes. *American Journal of Translational Research*. **5**(4), 379–392. ISSN 1943-8141.
HÄNNINEN, Arno, Raine TOIVONEN, Sakari PÖYSTI, Clara BELZER, Hubert PLOVIER, Janneke P. OUWERKERK, Rohini EMANI, Patrice D. CANI a Willem M. DE VOS, 2018. Akkermansia muciniphila induces gut microbiota remodelling and controls islet autoimmunity in NOD mice. *Gut* [online]. **67**(8), 1445–1453. ISSN 1468-3288. Dostupné z: doi:10.1136/gutjnl-2017-314508
HANSEN, Axel Kornerup, Fengjun LING, Anne KAAS, David P. FUNDA, Helene FARLOV a Karsten BUSCHARD, 2006. Diabetes preventive gluten-free diet decreases the number of caecal bacteria in non-obese diabetic mice. *Diabetes/Metabolism Research and Reviews*

[online]. **22**(3), 220–225. ISSN 1520-7552. Dostupné z: doi:10.1002/dmrr.609
HARRISON, Leonard C., 2005. The prospect of vaccination to prevent type 1 diabetes. *Human Vaccines* [online]. **1**(4), 143–150. ISSN 1554-8600. Dostupné z: doi:10.4161/hv.1.4.1923
HASKINS, Kathryn, Brenda BRADLEY, Katherine POWERS, Valerie FADOK, Sonia FLORES, Xiaofeng LING, Subbiah PUGAZHENTHI, Jane REUSCH a Jennifer KENCH, 2003. Oxidative stress in type 1 diabetes. *Annals of the New York Academy of Sciences* [online]. **1005**, 43–54. ISSN 0077-8923. Dostupné z: doi:10.1196/annals.1288.006
HASTINGS, Michael H., Akhilesh B. REDDY a Elizabeth S. MAYWOOD, 2003. A clockwork web: circadian timing in brain and periphery, in health and disease. *Nature Reviews. Neuroscience* [online]. **4**(8), 649–661. ISSN 1471-003X. Dostupné z: doi:10.1038/nrn1177
HAUPT-JORGENSEN, Martin, Laurits J. HOLM, Knud JOSEFSEN a Karsten BUSCHARD, 2018. Possible Prevention of Diabetes with a Gluten-Free Diet. *Nutrients* [online]. **10**(11). ISSN 2072-6643. Dostupné z: doi:10.3390/nu10111746
HE, Chen-Xia, Nicolas PREVOT, Christian BOITARD, Philip AVNER a Ute C. ROGNER, 2010. Inhibition of type 1 diabetes by upregulation of the circadian rhythm-related aryl hydrocarbon receptor nuclear translocator-like 2. *Immunogenetics* [online]. **62**(9), 585–592. ISSN 1432-1211. Dostupné z: doi:10.1007/s00251-010-0467-7
HE, Wei, Jeremy J. RACINE, Heather F. JOHNSTON, Xiaofan LI, Nainong LI, Kaniel CASSADY, Can LIU, Ruishu DENG, Paul MARTIN, Stephen FORMAN a Defu ZENG, 2014. Depletion of host CCR7+ Dendritic Cells Prevented Donor T cell Tissue Tropism in Anti-CD3-Conditioned Recipients. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* [online]. **20**(7), 920–928. ISSN 1083-8791. Dostupné z: doi:10.1016/j.bbmt.2014.03.029
HOFMANN, K., U. SCHÖNERSTEDT, E. MÜHLBAUER, D. WEDEKIND a E. PESCHKE, 2013. Clock gene expression in the liver of streptozotocin-induced and spontaneous type 1 diabetic rats. *Hormone and Metabolic Research = Hormon- Und Stoffwechselforschung = Hormones Et Metabolisme* [online]. **45**(9), 629–639. ISSN 1439-4286. Dostupné z: doi:10.1055/s-0033-1343462
HÖGLUND, P., J. MINTERN, C. WALTZINGER, W. HEATH, C. BENOIST a D. MATHIS, 1999. Initiation of autoimmune diabetes by developmentally regulated presentation of islet cell antigens in the pancreatic lymph nodes. *The Journal of Experimental Medicine* [online]. **189**(2), 331–339. ISSN 0022-1007. Dostupné z: doi:10.1084/jem.189.2.331
HONKANEN, Hanna, Sami OIKARINEN, Noora NURMINEN, Olli H. LAITINEN, Heini HUHTALA, Jussi LEHTONEN, Tanja RUOKORANTA, Minna M. HANKANIEMI, Valérie LECOUTURIER, Jeffrey W. ALMOND, Sisko TAURIAINEN, Olli SIMELL, Jorma ILONEN, Riitta VEIJOLA, Hanna VISKARI, Mikael KNIP a Heikki HYÖTY, 2017. Detection of enteroviruses in stools precedes islet autoimmunity by several months: possible evidence for slowly operating mechanisms in virus-induced autoimmunity. *Diabetologia* [online]. **60**(3), 424–431. ISSN 0012-186X, 1432-0428. Dostupné z: doi:10.1007/s00125-016-4177-z
HOORFAR, J., K. BUSCHARD a F. DAGNAES-HANSEN, 1993. Prophylactic nutritional modification of the incidence of diabetes in autoimmune non-obese diabetic (NOD) mice. *The British Journal of Nutrition* [online]. **69**(2), 597–607. ISSN 0007-1145. Dostupné z: doi:10.1079/bjn19930059
HULL, Caroline M., Mark PEAKMAN a Timothy I. M. TREE, 2017. Regulatory T cell dysfunction in type 1 diabetes: what's broken and how can we fix it? *Diabetologia* [online]. **60**(10), 1839–1850. ISSN 1432-0428. Dostupné z: doi:10.1007/s00125-017-4377-1
HUNG, Ming-Shiu, Philip AVNER a Ute Christine ROGNER, 2006. Identification of the transcription factor ARNTL2 as a candidate gene for the type 1 diabetes locus Idd6. *Human Molecular Genetics* [online]. **15**(18), 2732–2742. ISSN 0964-6906. Dostupné z: doi:10.1093/hmg/ddl209

HYÖTY, Heikki, Francisco LEON a Mikael KNIP, 2018. Developing a vaccine for type 1 diabetes by targeting coxsackievirus B. *Expert Review of Vaccines* [online]. **17**(12), 1071–1083. ISSN 1744-8395. Dostupné z: doi:10.1080/14760584.2018.1548281
CHAKIR, H., D. E. LEFEBVRE, H. WANG, E. CARAHER a F. W. SCOTT, 2005. Wheat protein-induced proinflammatory T helper 1 bias in mesenteric lymph nodes of young diabetes-prone rats. *Diabetologia* [online]. **48**(8), 1576–1584. ISSN 1432-0428. Dostupné z: doi:10.1007/s00125-005-1842-z
CHANG, T. J., H. H. LEI, J. I. YEH, K. C. CHIU, K. C. LEE, M. C. CHEN, T. Y. TAI a L. M. CHUANG, 2000. Vitamin D receptor gene polymorphisms influence susceptibility to type 1 diabetes mellitus in the Taiwanese population. *Clinical Endocrinology* [online]. **52**(5), 575–580. ISSN 0300-0664. Dostupné z: doi:10.1046/j.1365-2265.2000.00985.x
ILONEN, Jorma, Johanna LEMPAINEN a Riitta VEIJOLA, 2019. The heterogeneous pathogenesis of type 1 diabetes mellitus. *Nature Reviews Endocrinology* [online]. **15**(11), 635–650. ISSN 1759-5037. Dostupné z: doi:10.1038/s41574-019-0254-y
INSEL, Richard a Mikael KNIP, 2018. Prospects for primary prevention of type 1 diabetes by restoring a disappearing microbe. *Pediatric Diabetes* [online]. **19**(8), 1400–1406. ISSN 1399-5448. Dostupné z: doi:10.1111/pedi.12756
IN'T VELD, Peter, 2014. Insulitis in human type 1 diabetes: a comparison between patients and animal models. *Seminars in Immunopathology* [online]. **36**(5), 569–579. ISSN 1863-2300. Dostupné z: doi:10.1007/s00281-014-0438-4
IWAKABE, K., M. SHIMADA, A. OHTA, T. YAHATA, Y. OHMI, S. HABU a T. NISHIMURA, 1998. The restraint stress drives a shift in Th1/Th2 balance toward Th2-dominant immunity in mice. *Immunology Letters* [online]. **62**(1), 39–43. ISSN 0165-2478. Dostupné z: doi:10.1016/s0165-2478(98)00021-2
JAAKKOLA, Ilkka, Sirpa JALKANEN a Arno HÄNNINEN, 2003. Diabetogenic T cells are primed both in pancreatic and gut-associated lymph nodes in NOD mice. *European Journal of Immunology* [online]. **33**(12), 3255–3264. ISSN 0014-2980. Dostupné z: doi:10.1002/eji.200324405
JABRI, Bana a Ludvig M. SOLLID, 2009. Tissue-mediated control of immunopathology in coeliac disease. *Nature Reviews. Immunology* [online]. **9**(12), 858–870. ISSN 1474-1741. Dostupné z: doi:10.1038/nri2670
KAMPE, J. C. Malzahn, T. H. COURTNEY a Y. LENG, 1989. Shape instabilities of plate-like structures—I. Experimental observations in heavily cold worked in situ composites. *Acta Metallurgica* [online]. **37**(7), 1735–1745. ISSN 0001-6160. Dostupné z: doi:10.1016/0001-6160(89)90059-X
KIBIRIGE, M., B. METCALF, R. RENUKA a T. J. WILKIN, 2003. Testing the accelerator hypothesis: the relationship between body mass and age at diagnosis of type 1 diabetes. *Diabetes Care* [online]. **26**(10), 2865–2870. ISSN 0149-5992. Dostupné z: doi:10.2337/diacare.26.10.2865
KIRSCH, D. M., M. BAUMGARTEN, T. DEUFEL, F. RINNINGER, W. KEMMLER a H. U. HÄRING, 1983. Catecholamine-induced insulin resistance of glucose transport in isolated rat adipocytes. *The Biochemical Journal* [online]. **216**(3), 737–745. ISSN 0264-6021. Dostupné z: doi:10.1042/bj2160737
KNIP, Mikael a Olli SIMELL, 2012. Environmental triggers of type 1 diabetes. *Cold Spring Harbor Perspectives in Medicine* [online]. **2**(7), a007690. ISSN 2157-1422. Dostupné z: doi:10.1101/cshperspect.a007690
KO, Caroline H. a Joseph S. TAKAHASHI, 2006. Molecular components of the mammalian circadian clock. *Human Molecular Genetics* [online]. **15 Spec No 2**, R271-277. ISSN 0964-6906. Dostupné z: doi:10.1093/hmg/ddl207
KOLB, H. a R. B. ELLIOTT, 1994. Increasing incidence of IDDM a consequence of improved

hygiene? *Diabetologia* [online]. **37**(7), 729. ISSN 0012-186X. Dostupné z: doi:10.1007/BF00417700
KOLB, H., V. KOLB-BACHOFEN a B. O. ROEP, 1995. Autoimmune versus inflammatory type I diabetes: a controversy? *Immunology Today* [online]. **16**(4), 170–172. ISSN 0167-5699. Dostupné z: doi:10.1016/0167-5699(95)80115-4
KRISHNAN, Smitha, Nicholas ALDEN a Kyongbum LEE, 2015. Pathways and Functions of Gut Microbiota Metabolism Impacting Host Physiology. *Current opinion in biotechnology* [online]. **36**, 137–145. ISSN 0958-1669. Dostupné z: doi:10.1016/j.copbio.2015.08.015
KUHN, Chantal, Alix BESANÇON, Sébastien LEMOINE, Sylvaine YOU, Cindy MARQUET, Sophie CANDON a Lucienne CHATENOUD, 2016. Regulatory mechanisms of immune tolerance in type 1 diabetes and their failures. *Journal of Autoimmunity* [online]. **71**, 69–77. ISSN 1095-9157. Dostupné z: doi:10.1016/j.jaut.2016.05.002
LEBAILLY, Basile, Chenxia HE a Ute C. ROGNER, 2014. Linking the circadian rhythm gene Arntl2 to interleukin 21 expression in type 1 diabetes. *Diabetes* [online]. **63**(6), 2148–2157. ISSN 1939-327X. Dostupné z: doi:10.2337/db13-1702
LUDVIGSSON, Johnny, 2006. Why diabetes incidence increases--a unifying theory. *Annals of the New York Academy of Sciences* [online]. **1079**, 374–382. ISSN 0077-8923. Dostupné z: doi:10.1196/annals.1375.058
LUND-BLIX, Nicolai A., German TAPIA, Karl MÅRILD, Anne Lise BRANTSAETER, Pål R. NJØLSTAD, Geir JONER, Torild SKRIVARHAUG, Ketil STØRDAL a Lars C. STENE, 2020. Maternal and child gluten intake and association with type 1 diabetes: The Norwegian Mother and Child Cohort Study. *PLoS medicine* [online]. **17**(3), e1003032. ISSN 1549-1676. Dostupné z: doi:10.1371/journal.pmed.1003032
MAIURI, Luigi, Carolina CIACCI, Ida RICCIARDELLI, Loredana VACCA, Valeria RAIA, Salvatore AURICCHIO, Jean PICARD, Mohamed OSMAN, Sonia QUARATINO a Marco LONDEI, 2003. Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease. *Lancet (London, England)* [online]. **362**(9377), 30–37. ISSN 1474-547X. Dostupné z: doi:10.1016/S0140-6736(03)13803-2
MAKINO, S., K. KUNIMOTO, Y. MURAOKA, Y. MIZUSHIMA, K. KATAGIRI a Y. TOCHINO, 1980. Breeding of a non-obese, diabetic strain of mice. *Jikken Dobutsu. Experimental Animals* [online]. **29**(1), 1–13. ISSN 0007-5124. Dostupné z: doi:10.1538/expanim1978.29.1_1
MANNERING, Stuart I., Anthony R. DI CARLUCCIO a Colleen M. ELSO, 2019. Neoepitopes: a new take on beta cell autoimmunity in type 1 diabetes. *Diabetologia* [online]. **62**(3), 351–356. ISSN 1432-0428. Dostupné z: doi:10.1007/s00125-018-4760-6
MARCHEVA, Biliana, Kathryn Moynihan RAMSEY, Ethan D. BUHR, Yumiko KOBAYASHI, Hong SU, Caroline H. KO, Ganka IVANOVA, Chiaki OMURA, Shelley MO, Martha H. VITATERNA, James P. LOPEZ, Louis H. PHILIPSON, Christopher A. BRADFIELD, Seth D. CROSBY, Lellean JEBAILEY, Xiaozhong WANG, Joseph S. TAKAHASHI a Joseph BASS, 2010. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature* [online]. **466**(7306), 627–631. ISSN 1476-4687. Dostupné z: doi:10.1038/nature09253
MARIETTA, Eric V., Andres M. GOMEZ, Carl YEOMAN, Ashenafi Y. TILAHUN, Chad R. CLARK, David H. LUCKEY, Joseph A. MURRAY, Bryan A. WHITE, Yogish C. KUDVA a Govindarajan RAJAGOPALAN, 2013. Low incidence of spontaneous type 1 diabetes in non-obese diabetic mice raised on gluten-free diets is associated with changes in the intestinal microbiome. *PloS One* [online]. **8**(11), e78687. ISSN 1932-6203. Dostupné z: doi:10.1371/journal.pone.0078687
MARRE, Meghan L., John W. MCGINTY, I.-Ting CHOW, Megan E. DENICOLA, Noah W. BECK, Sally C. KENT, Alvin C. POWERS, Rita BOTTINO, David M. HARLAN, Carla J.

GREENBAUM, William W. KWOK, Jon D. PIGANELLI a Eddie A. JAMES, 2018. Modifying Enzymes Are Elicited by ER Stress, Generating Epitopes That Are Selectively Recognized by CD4+ T Cells in Patients With Type 1 Diabetes. *Diabetes* [online]. **67**(7), 1356–1368. ISSN 0012-1797, 1939-327X. Dostupné z: doi:10.2337/db17-1166
MARX, Alexander, Yosuke YAMADA, Katja SIMON-KELLER, Berthold SCHALKE, Nick WILLCOX, Philipp STRÖBEL a Cleo-Aron WEIS, 2021. Thymus and autoimmunity. *Seminars in Immunopathology* [online]. **43**(1), 45–64. ISSN 1863-2300. Dostupné z: doi:10.1007/s00281-021-00842-3
MATTSON, Mark P., David B. ALLISON, Luigi FONTANA, Michelle HARVIE, Valter D. LONGO, Willy J. MALAISSE, Michael MOSLEY, Lucia NOTTERPEK, Eric RAVUSSIN, Frank A. J. L. SCHEER, Thomas N. SEYFRIED, Krista A. VARADY a Satchidananda PANDA, 2014. Meal frequency and timing in health and disease. *Proceedings of the National Academy of Sciences of the United States of America* [online]. **111**(47), 16647–16653. ISSN 1091-6490. Dostupné z: doi:10.1073/pnas.1413965111
MAURANO, F., G. MAZZARELLA, D. LUONGO, R. STEFANILE, R. D'ARIENZO, M. ROSSI, S. AURICCHIO a R. TRONCONE, 2005. Small intestinal enteropathy in non-obese diabetic mice fed a diet containing wheat. *Diabetologia* [online]. **48**(5), 931–937. ISSN 0012-186X. Dostupné z: doi:10.1007/s00125-005-1718-2
MBONGUE, Jacques C., Jeffrey RAWSON, Pablo A. GARCIA, Nelson GONZALEZ, Jacob COBB, Fouad KANDEEL, Kevin FERRERI a Mohamed I. HUSSEINY, 2019. Reversal of New Onset Type 1 Diabetes by Oral Salmonella-Based Combination Therapy and Mediated by Regulatory T-Cells in NOD Mice. *Frontiers in Immunology* [online]. **10**, 320. ISSN 1664-3224. Dostupné z: doi:10.3389/fimmu.2019.00320
MCGUIRE, Helen M., Alexis VOGELZANG, Natasha HILL, Malin FLODSTRÖM-TULLBERG, Jonathan SPRENT a Cecile KING, 2009. Loss of parity between IL-2 and IL-21 in the NOD Idd3 locus. *Proceedings of the National Academy of Sciences of the United States of America* [online]. **106**(46), 19438–19443. ISSN 1091-6490. Dostupné z: doi:10.1073/pnas.0903561106
MIRANDA, Mariana Camila Gonçalves, Rafael Pires OLIVEIRA, Lícia TORRES, Sarah Leão Fiorini AGUIAR, Natalia PINHEIRO-ROSA, Luísa LEMOS, Mauro Andrade GUIMARÃES, Daniela REIS, Tatiany SILVEIRA, Ênio FERREIRA, Thaís Garcias MOREIRA, Denise Carmona CARA, Tatiani Uceli MAIOLI, Brian L. KELSALL, Daniela CARLOS a Ana Maria Caetano FARIA, 2019. Frontline Science: Abnormalities in the gut mucosa of non-obese diabetic mice precede the onset of type 1 diabetes. *Journal of Leukocyte Biology* [online]. **106**(3), 513–529. ISSN 1938-3673. Dostupné z: doi:10.1002/JLB.3HI0119-024RR
MISHRA, Sidharth Prasad, Shaohua WANG, Ravinder NAGPAL, Brandi MILLER, Ria SINGH, Subhash TARAPHDER a Hariom YADAV, 2019. Probiotics and Prebiotics for the Amelioration of Type 1 Diabetes: Present and Future Perspectives. *Microorganisms* [online]. **7**(3). ISSN 2076-2607. Dostupné z: doi:10.3390/microorganisms7030067
MOHAWK, Jennifer A., Carla B. GREEN a Joseph S. TAKAHASHI, 2012. Central and peripheral circadian clocks in mammals. *Annual Review of Neuroscience* [online]. **35**, 445–462. ISSN 1545-4126. Dostupné z: doi:10.1146/annurev-neuro-060909-153128
MUNGER, Kassandra L., Lynn I. LEVIN, Bruce W. HOLLIS, Noel S. HOWARD a Alberto ASCHERIO, 2006. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* [online]. **296**(23), 2832–2838. ISSN 1538-3598. Dostupné z: doi:10.1001/jama.296.23.2832
MURRI, Mora, Isabel LEIVA, Juan Miguel GOMEZ-ZUMAQUERO, Francisco J. TINAHONES, Fernando CARDONA, Federico SORIGUER a María Isabel QUEIPO-ORTUÑO, 2013. Gut microbiota in children with type 1 diabetes differs from that in healthy children: a case-control study. *BMC medicine* [online]. **11**, 46. ISSN 1741-7015. Dostupné z: doi:10.1186/1741-7015-11-46

NARASIMAMURTHY, Rajesh, Megumi HATORI, Surendra K. NAYAK, Fei LIU, Satchidananda PANDA a Inder M. VERMA, 2012. Circadian clock protein cryptochrome regulates the expression of proinflammatory cytokines. *Proceedings of the National Academy of Sciences of the United States of America* [online]. **109**(31), 12662–12667. ISSN 1091-6490. Dostupné z: doi:10.1073/pnas.1209965109
NEUMAN, Vit, Stepanka PRUHOVA, Michal KULICH, Stanislava KOLOUSKOVA, Jan VOSAHLO, Martina ROMANOVA, Lenka PETRUZELKOVA, Barbora OBERMANNOVA, David P. FUNDA, Ondrej CINEK a Zdenek SUMNIK, 2020. Gluten-free diet in children with recent-onset type 1 diabetes: A 12-month intervention trial. *Diabetes, Obesity & Metabolism* [online]. **22**(5), 866–872. ISSN 1463-1326. Dostupné z: doi:10.1111/dom.13974
NIKULINA, Marina, Christiane HABICH, Stefanie B. FLOHÉ, Fraser W. SCOTT a Hubert KOLB, 2004. Wheat Gluten Causes Dendritic Cell Maturation and Chemokine Secretion. *The Journal of Immunology* [online]. **173**(3), 1925–1933. ISSN 0022-1767, 1550-6606. Dostupné z: doi:10.4049/jimmunol.173.3.1925
NOBLE, Janelle A. a Henry A. ERLICH, 2012. Genetics of type 1 diabetes. *Cold Spring Harbor Perspectives in Medicine* [online]. **2**(1), a007732. ISSN 2157-1422. Dostupné z: doi:10.1101/cshperspect.a007732
NORRIS, J. M., B. BEATY, G. KLINGENSMITH, null YU LIPING, M. HOFFMAN, H. P. CHASE, H. A. ERLICH, R. F. HAMMAN, G. S. EISENBARTH a M. REWERS, 1996. Lack of association between early exposure to cow's milk protein and beta-cell autoimmunity. Diabetes Autoimmunity Study in the Young (DAISY). *JAMA* [online]. **276**(8), 609–614. ISSN 0098-7484. Dostupné z: doi:10.1001/jama.1996.03540080031025
ODEGARD, Jared M., Gerald T. NEPOM a Erik WAMBRE, 2015. Biomarkers for antigen immunotherapy in allergy and type 1 diabetes. *Clinical Immunology (Orlando, Fla.)* [online]. **161**(1), 44–50. ISSN 1521-7035. Dostupné z: doi:10.1016/j.clim.2015.05.023
ONENGUT-GUMUSCU, Suna, Wei-Min CHEN, Oliver BURREN, Nick J. COOPER, Aaron R. QUINLAN, Josyf C. MYCHALECKYJ, Emily FARBER, Jessica K. BONNIE, Michal SZPAK, Ellen SCHOFIELD, Premanand ACHUTHAN, Hui GUO, Mary D. FORTUNE, Helen STEVENS, Neil M. WALKER, Lucas D. WARD, Anshul KUNDAJE, Manolis KELLIS, Mark J. DALY, Jeffrey C. BARRETT, Jason D. COOPER, Panos DELOUKAS, TYPE 1 DIABETES GENETICS CONSORTIUM, John A. TODD, Chris WALLACE, Patrick CONCANNON a Stephen S. RICH, 2015. Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers. *Nature Genetics* [online]. **47**(4), 381–386. ISSN 1546-1718. Dostupné z: doi:10.1038/ng.3245
ONKAMO, P., S. VÄÄNÄNEN, M. KARVONEN a J. TUOMILEHTO, 1999. Worldwide increase in incidence of Type I diabetes--the analysis of the data on published incidence trends. *Diabetologia* [online]. **42**(12), 1395–1403. ISSN 0012-186X. Dostupné z: doi:10.1007/s001250051309
PANI, M. A., M. KNAPP, H. DONNER, J. BRAUN, M. P. BAUR, K. H. USADEL a K. BADENHOOP, 2000. Vitamin D receptor allele combinations influence genetic susceptibility to type 1 diabetes in Germans. *Diabetes* [online]. **49**(3), 504–507. ISSN 0012-1797. Dostupné z: doi:10.2337/diabetes.49.3.504
PATTERSON, Christopher C., Gisela G. DAHLQUIST, Eva GYÜRÜS, Anders GREEN, Gyula SOLTÉSZ, a EURODIAB STUDY GROUP, 2009. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet (London, England)* [online]. **373**(9680), 2027–2033. ISSN 1474-547X. Dostupné z: doi:10.1016/S0140-6736(09)60568-7
PATTERSON, Christopher C., Suvi KARURANGA, Paraskevi SALPEA, Pouya SAEEDI, Gisela DAHLQUIST, Gyula SOLTESZ a Graham D. OGLE, 2019. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from

the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice* [online]. **157**, 107842. ISSN 1872-8227. Dostupné z: doi:10.1016/j.diabres.2019.107842
PAUN, Alexandra, Christopher YAU a Jayne S. DANSKA, 2017. The Influence of the Microbiome on Type 1 Diabetes. *Journal of Immunology (Baltimore, Md.: 1950)* [online]. **198**(2), 590–595. ISSN 1550-6606. Dostupné z: doi:10.4049/jimmunol.1601519
PEARSON, James A., F. Susan WONG a Li WEN, 2016. The importance of the Non Obese Diabetic (NOD) mouse model in autoimmune diabetes. *Journal of Autoimmunity* [online]. **66**, 76–88. ISSN 1095-9157. Dostupné z: doi:10.1016/j.jaut.2015.08.019
POZZILLI, P., A. SIGNORE, A. J. WILLIAMS a P. E. BEALES, 1993. NOD mouse colonies around the world--recent facts and figures. *Immunology Today* [online]. **14**(5), 193–196. ISSN 0167-5699. Dostupné z: doi:10.1016/0167-5699(93)90160-M
QIAO, Yong-Chao, Jian SHEN, Xue-Zhi HONG, Ling LIANG, Chao-Sheng BO, Yi SUI a Hai-Lu ZHAO, 2016. Changes of regulatory T cells, transforming growth factor-beta and interleukin-10 in patients with type 1 diabetes mellitus: A systematic review and meta-analysis. *Clinical Immunology (Orlando, Fla.)* [online]. **170**, 61–69. ISSN 1521-7035. Dostupné z: doi:10.1016/j.clim.2016.08.004
RAMÍREZ, F., D. J. FOWELL, M. PUKLAVEC, S. SIMMONDS a D. MASON, 1996. Glucocorticoids promote a TH2 cytokine response by CD4+ T cells in vitro. *Journal of Immunology (Baltimore, Md.: 1950)*. **156**(7), 2406–2412. ISSN 0022-1767.
REDDY, Akhilesh B. a John S. O'NEILL, 2010. Healthy clocks, healthy body, healthy mind. *Trends in Cell Biology* [online]. **20**(1), 36–44. ISSN 1879-3088. Dostupné z: doi:10.1016/j.tcb.2009.10.005
REWERS, Marian a Johnny LUDVIGSSON, 2016. Environmental risk factors for type 1 diabetes. *Lancet (London, England)* [online]. **387**(10035), 2340–2348. ISSN 1474-547X. Dostupné z: doi:10.1016/S0140-6736(16)30507-4
RIDAURA, Vanessa K., Jeremiah J. FAITH, Federico E. REY, Jiye CHENG, Alexis E. DUNCAN, Andrew L. KAU, Nicholas W. GRIFFIN, Vincent LOMBARD, Bernard HENRISSAT, James R. BAIN, Michael J. MUEHLBAUER, Olga ILKAYEVA, Clay F. SEMENKOVICH, Katsuhiko FUNAI, David K. HAYASHI, Barbara J. LYLE, Margaret C. MARTINI, Luke K. URSELL, Jose C. CLEMENTE, William VAN TREUREN, William A. WALTERS, Rob KNIGHT, Christopher B. NEWGARD, Andrew C. HEATH a Jeffrey I. GORDON, 2013. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science (New York, N.Y.)* [online]. **341**(6150), 1241214. ISSN 1095-9203. Dostupné z: doi:10.1126/science.1241214
RIGBY, Mark R., Kristina M. HARRIS, Ashley PINCKNEY, Linda A. DIMEGLIO, Marc S. RENDELL, Eric I. FELNER, Jean M. DOSTOU, Stephen E. GITELMAN, Kurt J. GRIFFIN, Eva TSALIKIAN, Peter A. GOTTLIEB, Carla J. GREENBAUM, Nicole A. SHERRY, Wayne V. MOORE, Roshanak MONZAVI, Steven M. WILLI, Philip RASKIN, Lynette KEYES-ELSTEIN, S. Alice LONG, Sai KANAPARTHI, Noha LIM, Deborah PHIPPARD, Carol L. SOPPE, Margret L. FITZGIBBON, James MCNAMARA, Gerald T. NEPOM a Mario R. EHLERS, 2015. Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. *The Journal of Clinical Investigation* [online]. **125**(8), 3285–3296. ISSN 1558-8238. Dostupné z: doi:10.1172/JCI81722
RICHARDSON, Sarah J., Teresa RODRIGUEZ-CALVO, Ivan C. GERLING, Clayton E. MATHEWS, John S. KADDIS, Mark A. RUSSELL, Marie ZEISSLER, Pia LEETE, Lars KROGVOLD, Knut DAHL-JØRGENSEN, Matthias VON HERRATH, Alberto PUGLIESE, Mark A. ATKINSON a Noel G. MORGAN, 2016. Islet cell hyperexpression of HLA class I antigens: a defining feature in type 1 diabetes. *Diabetologia* [online]. **59**(11), 2448–2458. ISSN 1432-0428. Dostupné z: doi:10.1007/s00125-016-4067-4

ROBERTSON, Catherine C. a Stephen S. RICH, 2018. Genetics of type 1 diabetes. *Current Opinion in Genetics & Development* [online]. **50**, 7–16. ISSN 1879-0380. Dostupné z: doi:10.1016/j.gde.2018.01.006
ROEP, Bart O., 2007. Are insights gained from NOD mice sufficient to guide clinical translation? Another inconvenient truth. *Annals of the New York Academy of Sciences* [online]. **1103**, 1–10. ISSN 0077-8923. Dostupné z: doi:10.1196/annals.1394.018
ROEP, Bart O. a Mark PEAKMAN, 2012. Antigen targets of type 1 diabetes autoimmunity. *Cold Spring Harbor Perspectives in Medicine* [online]. **2**(4), a007781. ISSN 2157-1422. Dostupné z: doi:10.1101/cshperspect.a007781
SAKAGUCHI, Shimon, Norihisa MIKAMI, James B. WING, Atsushi TANAKA, Kenji ICHIYAMA a Naganari OHKURA, 2020. Regulatory T Cells and Human Disease. *Annual Review of Immunology* [online]. **38**, 541–566. ISSN 1545-3278. Dostupné z: doi:10.1146/annurev-immunol-042718-041717
SÁNCHEZ, Ester, Giada DE PALMA, Amalia CAPILLA, Esther NOVA, Tamara POZO, Gemma CASTILLEJO, Vicente VAREA, Ascensión MARCOS, José Antonio GARROTE, Isabel POLANCO, Ana LÓPEZ, Carmen RIBES-KONINCKX, Maria Dolores GARCÍA-NOVO, Carmen CALVO, Luis ORTIGOSA, Francesc PALAU a Yolanda SANZ, 2011. Influence of Environmental and Genetic Factors Linked to Celiac Disease Risk on Infant Gut Colonization by Bacteroides Species ▿ . *Applied and Environmental Microbiology* [online]. **77**(15), 5316–5323. ISSN 0099-2240. Dostupné z: doi:10.1128/AEM.00365-11
SAVILL, J., 1997. Apoptosis in resolution of inflammation. *Journal of Leukocyte Biology* [online]. **61**(4), 375–380. ISSN 0741-5400. Dostupné z: doi:10.1002/jlb.61.4.375
SCOTT, F. W., 1996. Food-induced type 1 diabetes in the BB rat. *Diabetes/Metabolism Reviews* [online]. **12**(4), 341–359. ISSN 0742-4221. Dostupné z: doi:10.1002/(SICI)1099-0895(199612)12:4<341::AID-DMR173>3.0.CO;2-O
SHAN, Lu, Øyvind MOLBERG, Isabelle PARROT, Felix HAUSCH, Ferda FILIZ, Gary M. GRAY, Ludvig M. SOLLID a Chaitan KHOSLA, 2002. Structural basis for gluten intolerance in celiac sprue. *Science (New York, N.Y.)* [online]. **297**(5590), 2275–2279. ISSN 1095-9203. Dostupné z: doi:10.1126/science.1074129
SHAO, Shiying, Fan HE, Yan YANG, Gang YUAN, Muxun ZHANG a Xuefeng YU, 2012. Th17 cells in type 1 diabetes. *Cellular Immunology* [online]. **280**(1), 16–21. ISSN 1090-2163. Dostupné z: doi:10.1016/j.cellimm.2012.11.001
SHARIF, Kassem, Abdulla WATAD, Louis COPLAN, Howard AMITAL, Yehuda SHOENFELD a Arnon AFEK, 2018. Psychological stress and type 1 diabetes mellitus: what is the link? *Expert Review of Clinical Immunology* [online]. **14**(12), 1081–1088. ISSN 1744-8409. Dostupné z: doi:10.1080/1744666X.2018.1538787
SHE, J. X., 1996. Susceptibility to type I diabetes: HLA-DQ and DR revisited. *Immunology Today* [online]. **17**(7), 323–329. ISSN 0167-5699. Dostupné z: doi:10.1016/0167-5699(96)10014-1
SILDORF, Stine Møller, Siri FREDHEIM, Jannet SVENSSON a Karsten BUSCHARD, 2012. Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus. *BMJ case reports* [online]. **2012**. ISSN 1757-790X. Dostupné z: doi:10.1136/bcr.02.2012.5878
SMYTH, Deborah J., Vincent PLAGNOL, Neil M. WALKER, Jason D. COOPER, Kate DOWNES, Jennie H. M. YANG, Joanna M. M. HOWSON, Helen STEVENS, Ross MCMANUS, Cisca WIJMENGA, Graham A. HEAP, Patrick C. DUBOIS, David G. CLAYTON, Karen A. HUNT, David A. VAN HEEL a John A. TODD, 2008. Shared and distinct genetic variants in type 1 diabetes and celiac disease. *The New England Journal of Medicine* [online]. **359**(26), 2767–2777. ISSN 1533-4406. Dostupné z: doi:10.1056/NEJMoa0807917

SOLLID, L. M., 2000. Molecular basis of celiac disease. *Annual Review of Immunology* [online]. **18**, 53–81. ISSN 0732-0582. Dostupné z: doi:10.1146/annurev.immunol.18.1.53
SPOLSKI, Rosanne, Mohit KASHYAP, Constance ROBINSON, Zuxi YU a Warren J. LEONARD, 2008. IL-21 signaling is critical for the development of type I diabetes in the NOD mouse. *Proceedings of the National Academy of Sciences of the United States of America* [online]. **105**(37), 14028–14033. ISSN 1091-6490. Dostupné z: doi:10.1073/pnas.0804358105
STECK, Andrea K. a Marian J. REWERS, 2011. Genetics of type 1 diabetes. *Clinical Chemistry* [online]. **57**(2), 176–185. ISSN 1530-8561. Dostupné z: doi:10.1373/clinchem.2010.148221
STEWARD, Charles A., Jose M. GONZALEZ, Steve TREVANION, Dan SHEPPARD, Giselle KERRY, James G. R. GILBERT, Linda S. WICKER, Jane ROGERS a Jennifer L. HARROW, 2013. The non-obese diabetic mouse sequence, annotation and variation resource: an aid for investigating type 1 diabetes. *Database: The Journal of Biological Databases and Curation* [online]. **2013**, bat032. ISSN 1758-0463. Dostupné z: doi:10.1093/database/bat032
TAN, Tingting, Yufei XIANG, Christopher CHANG a Zhiguang ZHOU, 2014. Alteration of regulatory T cells in type 1 diabetes mellitus: a comprehensive review. *Clinical Reviews in Allergy & Immunology* [online]. **47**(2), 234–243. ISSN 1559-0267. Dostupné z: doi:10.1007/s12016-014-8440-0
TSATSOULIS, Agathocles, 2006. The role of stress in the clinical expression of thyroid autoimmunity. *Annals of the New York Academy of Sciences* [online]. **1088**, 382–395. ISSN 0077-8923. Dostupné z: doi:10.1196/annals.1366.015
TSUI, Hubert, Yin CHAN, Lan TANG, Shawn WINER, Roy K. CHEUNG, Geoffrey PALTSER, Thirumahal SELVANANTHAM, Alisha R. ELFORD, James R. ELLIS, Dorothy J. BECKER, Pamela S. OHASHI a Hans-Michael DOSCH, 2008. Targeting of pancreatic glia in type 1 diabetes. *Diabetes* [online]. **57**(4), 918–928. ISSN 1939-327X. Dostupné z: doi:10.2337/db07-0226
VAARALA, Outi, Mark A. ATKINSON a Josef NEU, 2008. The „perfect storm" for type 1 diabetes: the complex interplay between intestinal microbiota, gut permeability, and mucosal immunity. *Diabetes* [online]. **57**(10), 2555–2562. ISSN 1939-327X. Dostupné z: doi:10.2337/db08-0331
VECCHIONE, Andrea, Roberta DI FONTE, Jolanda GEROSA, Tatiana JOFRA, Maria Pia CICALESE, Vincenzo NAPOLEONE, Elio IPPOLITO, Giuseppe GALVANI, Francesca RAGOGNA, Angela STABILINI, Eleonora BIANCONI, Pauline GROGAN, Clara BONURA, Riccardo BONFANTI, Giulio FRONTINO, Rita NANO, Raffaela MELZI, Maurizio DE PELLEGRIN, Andrea LAURENZI, Franco MESCHI, Graziano BARERA, Andrea RIGAMONTI, Rita INDIRLI, Emanuele BOSI, Lorenzo PIEMONTI, Alessandro AIUTI, Manuela BATTAGLIA a Georgia FOUSTERI, 2020. Reduced PD-1 expression on circulating follicular and conventional FOXP3+ Treg cells in children with new onset type 1 diabetes and autoantibody-positive at-risk children. *Clinical Immunology (Orlando, Fla.)* [online]. **211**, 108319. ISSN 1521-7035. Dostupné z: doi:10.1016/j.clim.2019.108319
VISSER, Jeroen, Jan ROZING, Anna SAPONE, Karen LAMMERS a Alessio FASANO, 2009. Tight junctions, intestinal permeability, and autoimmunity: celiac disease and type 1 diabetes paradigms. *Annals of the New York Academy of Sciences* [online]. **1165**, 195–205. ISSN 1749-6632. Dostupné z: doi:10.1111/j.1749-6632.2009.04037.x
VOIGT, Robin M., Christopher B. FORSYTH, Stefan J. GREEN, Ece MUTLU, Phillip ENGEN, Martha H. VITATERNA, Fred W. TUREK a Ali KESHAVARZIAN, 2014. Circadian disorganization alters intestinal microbiota. *PloS One* [online]. **9**(5), e97500. ISSN 1932-6203. Dostupné z: doi:10.1371/journal.pone.0097500
WALKER, L. S. K. a M. VON HERRATH, 2016. CD4 T cell differentiation in type 1 diabetes. *Clinical and Experimental Immunology* [online]. **183**(1), 16–29. ISSN 1365-2249. Dostupné

z: doi:10.1111/cei.12672
WÅLLBERG, Maja a Anne COOKE, 2013. Immune mechanisms in type 1 diabetes. *Trends in Immunology* [online]. **34**(12), 583–591. ISSN 1471-4981. Dostupné z: doi:10.1016/j.it.2013.08.005
WELSH, David K., Joseph S. TAKAHASHI a Steve A. KAY, 2010. Suprachiasmatic nucleus: cell autonomy and network properties. *Annual Review of Physiology* [online]. **72**, 551–577. ISSN 1545-1585. Dostupné z: doi:10.1146/annurev-physiol-021909-135919
WEN, Li, Ruth E. LEY, Pavel Yu VOLCHKOV, Peter B. STRANGES, Lia AVANESYAN, Austin C. STONEBRAKER, Changyun HU, F. Susan WONG, Gregory L. SZOT, Jeffrey A. BLUESTONE, Jeffrey I. GORDON a Alexander V. CHERVONSKY, 2008. Innate immunity and intestinal microbiota in the development of Type 1 diabetes. *Nature* [online]. **455**(7216), 1109–1113. ISSN 1476-4687. Dostupné z: doi:10.1038/nature07336
WILBERZ, S., H. J. PARTKE, F. DAGNAES-HANSEN a L. HERBERG, 1991. Persistent MHV (mouse hepatitis virus) infection reduces the incidence of diabetes mellitus in non-obese diabetic mice. *Diabetologia* [online]. **34**(1), 2–5. ISSN 0012-186X. Dostupné z: doi:10.1007/BF00404016
WILKIN, T. J., 2001. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. *Diabetologia* [online]. **44**(7), 914–922. ISSN 1432-0428. Dostupné z: doi:10.1007/s001250100548
WOOD HEICKMAN, Lauren K., Mark D. DEBOER a Alessio FASANO, 2020. Zonulin as a potential putative biomarker of risk for shared type 1 diabetes and celiac disease autoimmunity. *Diabetes/Metabolism Research and Reviews* [online]. **36**(5), e3309. ISSN 1520-7560. Dostupné z: doi:10.1002/dmrr.3309
Y, Naito, Uchiyama K a Takagi T, 2018. A next-generation beneficial microbe: *Akkermansia muciniphila*. *Journal of Clinical Biochemistry and Nutrition* [online]. **63**(1), 33–35. ISSN 0912-0009, 1880-5086. Dostupné z: doi:10.3164/jcbn.18-57
YAGI, H., M. MATSUMOTO, K. KUNIMOTO, J. KAWAGUCHI, S. MAKINO a M. HARADA, 1992. Analysis of the roles of CD4+ and CD8+ T cells in autoimmune diabetes of NOD mice using transfer to NOD athymic nude mice. *European Journal of Immunology* [online]. **22**(9), 2387–2393. ISSN 0014-2980. Dostupné z: doi:10.1002/eji.1830220931
YOO, Seung-Hee, Shin YAMAZAKI, Phillip L. LOWREY, Kazuhiro SHIMOMURA, Caroline H. KO, Ethan D. BUHR, Sandra M. SIEPKA, Hee-Kyung HONG, Won Jun OH, Ook Joon YOO, Michael MENAKER a Joseph S. TAKAHASHI, 2004. PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *Proceedings of the National Academy of Sciences of the United States of America* [online]. **101**(15), 5339–5346. ISSN 0027-8424. Dostupné z: doi:10.1073/pnas.0308709101
YOUNGSTEDT, Shawn D., Christopher E. KLINE, Jeffrey A. ELLIOTT, Mark R. ZIELINSKI, Tina M. DEVLIN a Teresa A. MOORE, 2016. Circadian Phase-Shifting Effects of Bright Light, Exercise, and Bright Light + Exercise. *Journal of Circadian Rhythms* [online]. **14**, 2. ISSN 1740-3391. Dostupné z: doi:10.5334/jcr.137
YSMAIL-DAHLOUK, Lamia, Wafa NOUARI a Mourad ARIBI, 2016. 1,25-dihydroxyvitamin D3 down-modulates the production of proinflammatory cytokines and nitric oxide and enhances the phosphorylation of monocyte-expressed STAT6 at the recent-onset type 1 diabetes. *Immunology Letters* [online]. **179**, 122–130. ISSN 1879-0542. Dostupné z: doi:10.1016/j.imlet.2016.10.002
YU, Hua, Nicola GAGLIANI, Harumichi ISHIGAME, Samuel HUBER, Shu ZHU, Enric ESPLUGUES, Kevan C. HEROLD, Li WEN a Richard A. FLAVELL, 2017. Intestinal type 1 regulatory T cells migrate to periphery to suppress diabetogenic T cells and prevent diabetes development. *Proceedings of the National Academy of Sciences of the United States of America*

[online]. **114**(39), 10443–10448. ISSN 1091-6490. Dostupné z: doi:10.1073/pnas.1705599114
YU, Xiaofei, Darcy ROLLINS, Kelly A. RUHN, Jeremy J. STUBBLEFIELD, Carla B. GREEN, Masaki KASHIWADA, Paul B. ROTHMAN, Joseph S. TAKAHASHI a Lora V. HOOPER, 2013. TH17 cell differentiation is regulated by the circadian clock. *Science (New York, N.Y.)* [online]. **342**(6159), 727–730. ISSN 1095-9203. Dostupné z: doi:10.1126/science.1243884
YURKOVETSKIY, Leonid, Michael BURROWS, Aly A. KHAN, Laura GRAHAM, Pavel VOLCHKOV, Lev BECKER, Dionysios ANTONOPOULOS, Yoshinori UMESAKI a Alexander V. CHERVONSKY, 2013. Gender bias in autoimmunity is influenced by microbiota. *Immunity* [online]. **39**(2), 400–412. ISSN 1097-4180. Dostupné z: doi:10.1016/j.immuni.2013.08.013
ZENG, Hanyu, Rong ZHANG, Boquan JIN a Lihua CHEN, 2015. Type 1 regulatory T cells: a new mechanism of peripheral immune tolerance. *Cellular & Molecular Immunology* [online]. **12**(5), 566–571. ISSN 2042-0226. Dostupné z: doi:10.1038/cmi.2015.44

ATTACHMENTS:

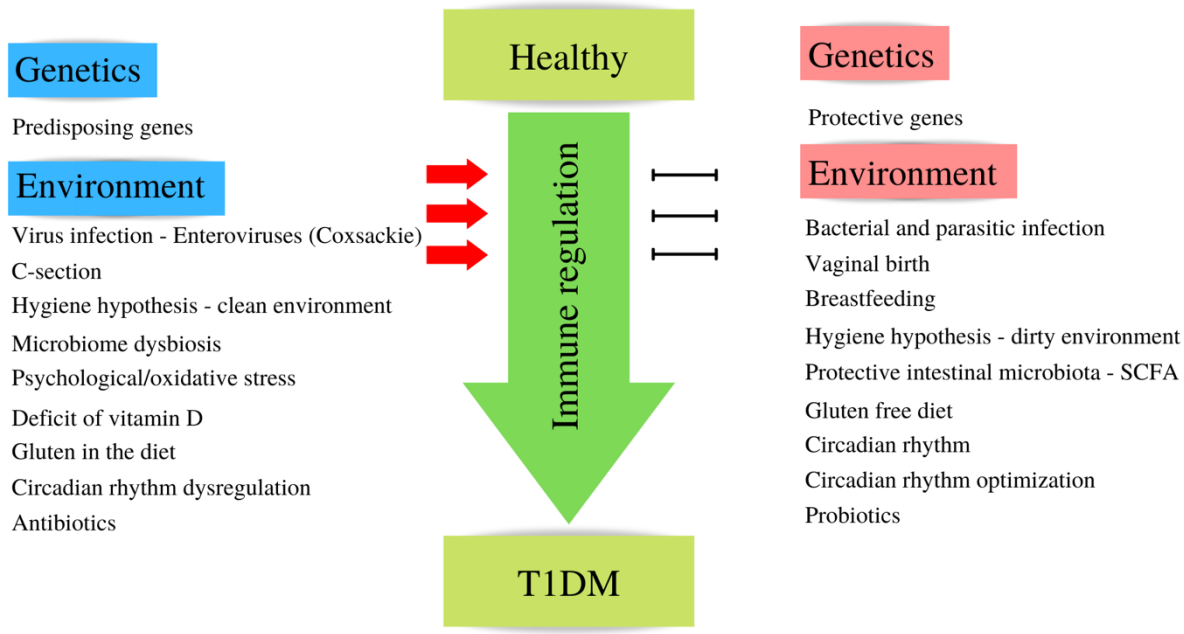

Figure 1: T1DM as a multifactorial autoimmune disease. Disease onset and development or disease prevention may be influenced through various environmental factors. There is also a certain relationship between the influence of genetics and the environment. These two arms altogether affect an immune balance, which shift may result in either protection or increased susceptibility to T1DM onset. Modified scheme from Antvorskov et al. (Antvorskov et al. 2014).