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Tolerogenic dendritic cells as immune interventions in prevention or therapy of type 1 diabetes

Tolerogenní dendritické buňky jako imunointervence v prevenci nebo terapii diabetu 1. typu

Bachelor´s thesis

Supervisor:

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Čestné prehlásenie

Prehlasujem, že som bakalársku prácu vypracovala samostatne a že som uviedla všetky použité informačné zdroje a literatúru. Táto práca ani jej podstatná časť nebola predložená na iný alebo rovnaký akademický titul.

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Poďakovanie

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Abstract

The main aim of this work is to refer a recent summary of the opportunities and pitfalls of the application of tolerogenic dendritic cells in the prevention or therapy of type 1 diabetes (T1D). Tolerogenic dendritic cells (TolDCs) represent a potential tool for the treatment of allergies, transplant rejections and autoimmune diseases, including T1D, due to their capability to specifically inhibit autoimmune reactions without causing general immunosuppression. TolDCs represent a specific group of dendritic cells and are essential in establishing central and peripheral tolerance. This work presents a helpful guide to better understanding the physiology of tolerogenic DCs and an overview of in vitro generation attempts. In addition, the route of application and migration to target organs has been described.

Type 1 diabetes (T1D) is a chronic disease resulting from immune-mediated destruction of the insulin-producing beta cells in the pancreas. Animal models have been invaluable in testing innovative medical treatments since the early testing of insulin in dogs almost a century ago. Animal models of type 1 diabetes (T1D) enable the study of the mechanisms underlying its pathogenesis and the potential development of therapeutic interventions. However, there are still significant gaps in our general understanding of type 1 diabetes and in our capability to reduce the complications and inconveniences associated with the disease.

Key words

Tolerogenic dendritic cells, type 1 diabetes, cell therapy, prevention, translational research, animal models

Abstrakt

Hlavným cieľom tejto práce je poskytnúť aktuálne zhrnutie možností a úskalí použitia tolerogénnych dendritických buniek v prevencii alebo terapii diabetu 1. typu (T1D). Tolerogénne dendritické bunky (TolDC) predstavujú potenciálny nástroj na liečbu alergií, odmietnutia transplantátu a autoimunitných ochorení vrátane T1D, vďaka ich schopnosti špecificky potláčať autoimunitné reakcie bez vyvolania celkovej imunosupresie. TolDC predstavujú špecifickú skupinu dendritických buniek a sú nevyhnutné pri vytváraní centrálnej a periférnej tolerancie. Práca poskytuje užitočný zdroj informácií na lepšie pochopenie biológie tolerogénnych dendritických buniek a prehľad o snahách o ich generovanie in vitro. Okrem toho bola opísaná cesta aplikácie a migrácie do cieľových orgánov.

Diabetes 1. typu (T1D) je chronické ochorenie spôsobené imunitne podmienenou deštrukciou beta buniek pankreasu, ktoré produkujú inzulín. Zvieracie modely sú neoceniteľné pri testovaní inovatívnych liečebných postupov už od prvých testov inzulínu na psoch pred takmer sto rokmi. Zvieracie modely diabetu 1. typu (T1D) umožňujú štúdium mechanizmov, ktoré sú základom jeho patogenézy a potenciálny vývoj terapeutických zásahov. V našom všeobecnom chápaní diabetu 1. typu a v našej schopnosti znížiť komplikácie a nepríjemnosti spojené s týmto ochorením však stále existujú značné medzery.

Kľúčové slová

Tolerogénne dendritické bunky, diabetes 1. typu, bunková terapia, prevencia, translačný výskum, zvieracie modely

Content

List of abbreviations

TolDCs	Tolerogenic dendritic cells
T1D	Type 1 Diabetes
DCS	Dendritic cells
APCs	Antigen-presenting cells
β-cells	beta cells
IL-2	Interleukin-2
DN	Diabetic Nephropathy
GFR	Glomerular filtration rate
NOD	Non-obese diabetic mice
Tregs	Regulatory T cells
i. v.	intravenosus
i.p.	intraperitoneal
s. c.	subcutaneous
PLNs	Pancreatic lymph nodes
HSCs	hematopoetic stem cells
HLA	Human Leucocyte Antigen
CTLA4	Cytotoxic T lymphocyte antigen 4
AT	antithrombin
CTS	The cataract Shionogi
MHC	Major histocompatibility complex
TGF- β	transforming growth factor β
IDO	indoleamine 2,3-dioxygenase
HO-1	heme oxygenase-1
PDL-1, 2	programmed cell death ligand- 1,2
ILT	immunoglobulin-like transcript
mDCs	myeloid DCs
TSLP	thymic stromal lymphopoietin
iDCs	immature DCs
PAMPs	Pathogen-associated molecular patterns
DAMPs	Damage-associated molecular patterns
GAD65	glutamic acid decarboxylase 65
HIPs	hybrid insulin peptides

MSCs	myeloid-derived suppressor cells
CCL19	C-C chemokine ligand 19
GM-CSF	granulocyte-macrophage colony-stimulating factor
VitD3	Vitamin D3
BMDC	bone marrow-derived dendritic cell
IFN	interferon
PGE2	Prostaglandin E 2
PB	peripheral blood
LPS	lipopolysacharide
Th1	T helper 1
FOXP3+ Tregs	Forkhead box P3 expressing Tregs
Tr1	Type 1 regulatory T (Tr1) cells
ZnT8	zinc transporter-8
IBD	inflammatory bowel disease

1. Introduction

Type 1 diabetes is a chronic, autoimmune disease marked by insulin deficiency resulting from beta cells (β-cells) destruction and subsequent hyperglycaemia. Ideas and knowledge of type 1 diabetes have expanded significantly over the past 25 years, leading to a better understanding of it´s mechanisms, epidemiology, genetics, immune and β-cell manifestations, and disease burden. Type 1 diabetes is associated with an enhanced incidence of islet-specific autoreactive CD8+ T lymphocytes and reduced adaptive immune control (DiMeglio et al. 2018).

Cell therapies involving tolerogenic DCs (tolDCs) constitute new emerging strategies for the therapy of autoimmune diseases such as T1D (Funda et al. 2019). Their important role in inducing and sustaining tolerance has been proven in experimental animal models (Obregon et al. 2017). In this work, tolDCs sets in the context of T1D therapy and the immune regulatory pathways facilitated by these cells are succinctly reviewed.

1.1. Diabetes type 1 and its incidence

Type 1 diabetes mellitus (T1D) is a multifactorial, autoimmune disease that is caused by the destruction of β-cells found in the islets of Langerhans in the pancreas. (Sarwar et al. 2010) The disease is characterized by a process in which certain pancreatic β-cell proteins are identified by the immune system as antigens, which are called autoantigens. Diabetes mellitus can manifest itself at any age, but it has a tendency to develop in childhood and is considered a state of insulin deficiency caused by the β-cell destruction of the pancreas (Atkinson et al. 2014).

T1D is considered an autoimmune disease rooted in T cell attack on insulin-producing β-cells. Especially recently, it is also thought to be the outcome of a complicated synergy of genetic factors and environmental factors (e.g. diet, viruses), the microbiome and metabolome, as well as genetic factors metabolic activity and, not least, the immune system, which vary from person to person. The most abundant immune cells in insulitic lesions are CD8+ T-lymphocytes, while CD4 T-lymphocytes are more rare, although relatively more common in the early stages of the development of the disease (Akil et al. 2021; Burrack et al. 2017; Oling et al. 2012). T1D is a polygenic disease and for many years over 40 or recently even over 50 risk gene markers have been described (Steck and Rewers 2011; Floyel et al. 2015).The most prominent loci and basis of the immunodeficiency disorder are within the major

histocompatibility complex (HLA) system. Specifically, these are the HLA DRB1 and DQB1 alleles. Individuals positive for HLA-DRB1*03 (DR3) or HLA-DRB1*04 (DR4) with DQB1*03:02 (DQ8) are most likely to develop T1D (Nguyen et al. 2013). The gene responsible for regulating antigen-presenting T cell activation and consequent cellular immunity is called CD28 and is located on chromosome 2. In addition, there is a cytotoxic T lymphocyte antigen 4 (CTLA4) gene that has also been mapped on chromosome 2. Its product CTLA4, expressed on activated T cells, is thought to be a permissive candidate gene in the context of CD28, which is implicated in the origin of autoimmune diseases (Wang et al. 2014).

Apart from genetic predispositions T1D is substantially influenced by environmental factors and recent changes in the environment. Evidence has been collected for factors affecting both the effector and regulatory arm of immune responses in T1D. Thus, while viruses such as rotavirus or Coxsackievirus B4 are suspected as possible initial triggering events in T1D (Harrison 2005), the interplay of dietary factors, microbiome changes, metabolic activity and gut permeability may influence T1D penetrance by affecting also the development of protective regulatory immune responses (Vaarala et al. 2008; Bach 2021; Bluestone et al. 2021).

T1D is so far irreversible and incurable in humans. Transplantation of pancreatic islets or even attempts of experimental β-cell neogenesis have not been successful unless persisting autoimmunity against β-cells is reset, e.g. high dose immunoablative chemotherapy and autologous hematopoietic stem cell transplantation (Gu et al. 2012). Prolonged strong immunosuppression, although may be effective, is not acceptable for the disease control. However, autologous hematopoietic stem cell transplantations have undergone a long pathway of development and they represent a promising therapeutical intervention for T1D therapy with lasting remission if used on a personalized basis (van Megen et al. 2018).

With respect to the theme of this thesis it is relevant to mention that application of tolerogenic dendritic cells (tolDCs) represent on or the few interventions that are capable of curing or reversing T1D in NOD mice (Creusot et al. 2010; Di Caro et al. 2014).

Another interesting recent approach in T1D research is the concept of neo-epitopes in the disease initiation and etiopathogenesis. It has been shown that post translationally modified epitopes of beta cells may trigger beta cell destruction (Mannering et al. 2005). The concept of neopitopes in T1D may give answers to questions like the escape from immune tolerance, the role of an environmental hit/stress and lack of regulatory influences in the beta cell specific autoimmunity (Mannering et al. 2018). New genetic studies are revealing processes involved

in the early development of the disease , e.g. in the cytokine system interleukin-2 (IL-2) and interleukin-1 (IL-1) (Todd 2010; Skowera et al. 2008). While the clinical picture of type 1 diabetes as a gradual decrease in β-cell function over the course of life and the requirement for daily insulin therapy for patient recovery have been evident for more than a century, the precise physiological, immunological (effector and regulatory) and genetic processes that contribute to the initiation of the disease and its natural history are still being elucidated (Bluestone et al. 2010; Bluestone et al. 2021).

Several lines of evidence documented, that the prevalence of type 1 diabetes is increasing, and increasing more than estimated worldwide. The total annual increase is estimated at around 3%. Today, an estimated 463 million adults and 1.1 million children and adolescents under 20 suffer from diabetes. Based on estimates, the IDF predicts that 578 million adults will have diabetes in 2030 and 700 million in 2045. Low to middle economic areas will experience the greatest increase in disease (IDF Diabetes Atlas, 2019). Especially in developing and underdeveloped countries, insulin may be more difficult to obtain and access to care tools, including lifestyle education, may be limited. This often leads to complications and premature death. The World Health Organization reports that diabetes will be the seventh most common cause of death by 2030 (Karamanou et al. 2016). Dramatic development of ketoacidosis occurs more rapidly in children because they are more susceptible to insulin deficiency than adults. Alternating ketoacidosis or hypoglycemia in young children negatively affect cognitive systems and structural abnormalities of the brain (Patterson et al. 2019).

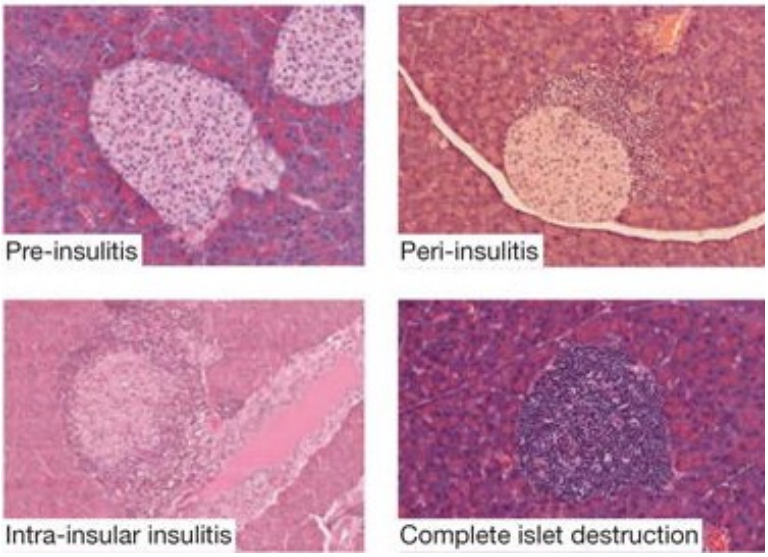

Figure 1. Markers of diabetes. Lymphocyte infiltration into islets of NOD mice is out of sync during the process of diabetes, with a normal mixture of normal healthy islets, peri-islet insulitis, intra-islet insulitis and full β-cell destruction (Reprinted and edited from Bluestone et al. 2010).

1.2. Impact on the human body

An acute fatal disease has turned into a chronic disease that can be compensated by exogenous insulin application. To achieve normal glucose levels, insulin also has, unfortunately, its disadvantages and limitations in addition to the risk of hypoglycaemia (Warshauer et al. 2019).

In diabetes, the body does not make enough insulin due to destroyed β-cells, or the target cells are unable to efficiently receive and use the insulin. This results in an increase in blood sugar concentration above a threshold level (Higuera 2019). The long-term effects of hyperglycemia on tissues and organs leads to the development of chronic complications of diabetes (Nathan 2015; Pelikánová et al. 2012). Hyperglycaemia is associated with several chronic medical complications including nephropathy (DN), diabetic retinopathy, neuropathy and macroangiopathy.

High glucose levels in the blood negatively influence the arteries in the body and the kidneys filter blood from them. When this occurs, the body begins to lose albumin through the urine- microalbuminuria, generally considered the most common phenotype of DN. Glomerular filtration rate (GFR) plays a role in assessing kidney function. The kidneys should ideally be working at 100% or have a GFR of 100. If tests prove that the GFR is 15-60%, kidney disease is present. Kidney damage takes place over several years until full nephropathy develops (Seymour 2019).

Regarding retinopathy, diabetes can damage almost all ocular structures, including: the oculomotor muscles, the retina, the intraocular lens and the optic nerve. If we focus on the retina, specifically damage to the retinal capillaries, this state appears to be the main reason for visual impairment in T1D patients. There are 2 main pathways in which vision is reduced: macular edema and proliferative retinopathy. Edema begins with damaged retinal blood vessels when fluid and protein leak out. Central vision is processed under the macula of the eye, where the sediments mentioned above are deposited. Conversely, proliferative retinopathy is related to retinal hypoxia, which is compensated by the formation of new, fragile blood vessels that are prone to bleeding and obstructing vision (Berco et al. 2015).

The prevalence of neuropathy varies depending on the severity and duration of hyperglycaemia (Edwards et al. 2008). Neuropathy manifests as nerve damage and contributes to the development of diabetic foot syndrome. Certain clinical autonomic signs, such as progression of leg muscle weakness or dryness of the legs resulting from reduced sweat flow, increase the consequent risk of ulceration, infection and amputation (Perkins 2020).

Long-term diabetes with bad metabolic management may be associated with microvascular and macrovascular diseases that accompany or maintain changes in coagulation factors (Forbes et al. 2013). Thrombin-induced variations represent subtle changes in the balance of haemostasis. The thrombin production measurement is sensitive to the deficiency of coagulation factors and determines the effect of anticoagulant drugs and deficiency of antithrombin (AT), protein C and other substances Or protein S and resistance to activated protein C. These variations in thrombin output are secondary effects of increased blood glucose levels, and insulin therapy reduces these irregularities (Jasser-Nitsche et al. 2020).

1.3. Life with diabetes

People suffering from T1D are usually diagnosed with the disease in childhood and it lasts for life (Freeborn et al. 2017). Children aged 8-11 years start to take on some of the tasks associated with diabetes treatment, until then their parents supervise them and are solely responsible for the correctness of the medication. For parents, the adjustment to life of a child with T1D is crucial, which often has a negative effect on the quality of life of the parent (Barnard et al. 2010). Minimizing or stopping chronic complications related to the heart, liver and kidneys can be achieved by monitoring carbohydrate intake, blood glucose levels and repeated insulin administration throughout the day (Freeborn et al. 2017). It is important to establish a therapeutic relationship between the doctor and the patient. Among psychological means, psychoeducation of the patient and his/her family is used and involves explaining the nature of the disorder, the course and treatment planning (Tůma 2014).

1.4. Past intervention (history)

The first description of the symptoms of diabetes dates back to antiquity, they were found in the Ebers Papyrus. The Greek physician A. Cappadocia of Cappadocia in the 2nd century gave the first description of the disease with unquenchable thirst associated with excessive urination treated with plant extracts. He called this disease diabetes.

In the 17th century, a sweet taste in urine called mellitus is discovered by Indian physicians. In the 19th century, pancreatic islets are discovered, differentiated into α-cells and β-cells. A close link between the pancreas and diabetes is established, although the function is not yet fully understood. Scientists O. Minkowski and Joseph von Mering conduct an experiment to surgically remove the pancreas in a dog. The result is the induction of diabetes and the subsequent death of the animal. They demonstrated that the pancreas is a gland important for maintaining glucose homeostasis.

The 20th century brought a medical breakthrough- the discovery of insulin, which responds to the body's use of sugars. The sugar-lowering substance was isolated from a canine pancreas in an experiment led by Frederick Banting and Charles Best. Subsequently, there were technical developments in insulin therapy, synthetic production of human insulin, purification and extraction of insulin, continuous dosing of insulin, and production of insulin analogues.

Testing insulin in humans was the next phase, with outstanding success. In 1922, the Lilly Pharmaceutical Company introduced Iletin, the world's first commercially available insulin (Karamanou et al. 2016).

2. Animal models of T1D

In the late 1970s and early 1980s, our coprehension of the molecular biology, etiology, and pathogenesis of T1D was advanced by the recognition of spontaneous animal models, most notably the NOD mouse (Makino et al. 1980) and BB Wistar rat (Nakhooda et al. 1978). These models allowed scientists to approach specific aspects of the disease. The use of the NOD mouse as a basis for preclinical research on diabetes was prompted by similarities with human autoimmune type 1. diabetes and the fact that BB rats are lymphopenic (Shoda et al. 2005; Van Belle et al. 2009). Mice and humans share a common polygenic predisposition to T1D, defects in immune control and the capacity to produce disease remission by bone marrow transplantation (Leiter & von Herrath 2004). Important differences between human T1D and the NOD model however exist. Several studies indicate a contrasting roles of maternal autoantibodies in mice and humans. Most notable perhaps is the prevalence and gender variation in the two types. It is crucial to remember that the immune systems of humans and mice differ dramatically (Mestas & Hughes 2004). Differences are also found in the cellular composition, function and gene expression within pancreatic islets (Brissova et al. 2005).

Most of our findings to date on personalized therapeutic approaches to T1D have been derived from animal model experiments, but a repeated topic in the therapeutic area of T1D is the poor correlation between promising outcomes in mice and the same results in humans (Akil 2021). In NOD mice, it has been possible to prevent disease by several interventions, that were however difficult to repeat in human trials (Funda et al. 2019; Hanninen & Harrison 2004; Harrison 2005). A widely used mouse models type 1. diabetes and Moody is the female nonobese diabetic (NOD) mouse, the Non-obese C57BL/6 mutant (Akita) mouse and most recently also humanized mice. (Van Belle et al. 2009).

2.1. Female non-obese diabetic (NOD) mouse

The origin of NOD is derived from the so-called cataract Shionogi (CTS) mouse- an inbred strain of mice with tiny eyes. Using their offspring, brother-sister mating was initiated and after the 20th generation, a mouse with polydipsia, polyuria and marked weight loss with normal fasting blood glucose levels emerged. With this unusual mouse, inbreeding proceeded and created an inbred strain with spontaneous diabetic development, now known as the NOD mouse (Makino et al. 1980; Katsuda et al. 2013).

The NOD mouse is significant mainly because it is able to spontaneously mature with partial penetrance, mirroring the vulnerability of T1D to additional environmental factors. Similar to human T1D, NOD mice have polygenic genetic vulnerability with a predominance of MHC genes. NOD mice predominate over human T1D progression by several differences. They are capable of longer survival after the onset of diabetes due to less severe ketoacidosis, thus allow experimental setup involving insulin treatment (Leiter et al. 1987; Pearson et al. 2016; Funda et al. 2019).

NOD mice show elevated levels of circulating autoreactive T lymphocytes (CD4+ and CD8+) and develop autoantibodies directed against analogues of B cell autoantigens. The current theory of the disease is based mainly on the study of the course of the disease in NOD mice. The initiation of inflammation occurs in individuals with genetic predisposition, which selectively affects the β-cells of the islets of Langerhans. In the initiation phase, natural immunity cells such as dendritic cells, macrophages along with autoreactive B lymphocytes accumulate in the pancreas. Antigen-presenting cells (APCs) present antigens to T lymphocytes from β-cells in the pancreatic lymph node where T lymphocyte activation occurs. After expansion, the autoreactive T lymphocytes migrate to the islets of Langerhans where they devastate the β-cells (Jaakkola et al. 2003; Bluestone et al. 2010).

2.2. Non-obese C57BL/6 mutant (Akita) mouse

The non-obese mutant mouse takes its name from the site of Akita colony discovery, is an autosomal dominant mode of heredity. Akita mice have a mutant locus on chromosome 7. Early in life, Akita mice exhibit diabetic symptoms such as polyuria, polydipsia and hyperglycaemia. Males are dominant in symptom production at this time. In contrast to NOD mice, a decrease in the density of active B cells was observed as early as 4 weeks, but in contrast there was no infiltration of lymphocytes. The mutation in Ins2 caused a confusion of amino acids in the insulin 2 gene, resulting in misfolding of the insulin protein. The consequence of this mutation there is a gradual reduction in ß-cell function in Akita mice (Yoshioka et al. 1997; Katsuda et al. 2013).

2.3. Humanized mice

Immunodeficient mice that are grafted with functional human cells and tissues are known as humanized mice. Human islets and grafts of human hematopoietic and immune systems are transplanted to humanized mice. The use of humanized mice is preferable because current mice have not shown significant results in human clinical studies. These mouse strains support grafting with hematopoietic stem cells (HSCs), functional human tissues, mature lymphocytes and islets (Greiner et al. 2011). These models are based on NOD scid mice that exhibit a target-specific mutation of the common gamma chain receptor IL2 (IL2rγ null). NOD scid IL2rγ null (NSG) mice have high levels of immunodeficiency and enable high rate of tissue attachment and functional human cells. This makes NSG mice perfect for studying the human body's function in vivo and to identify mechanisms of action of therapeutic interventions (Shultz et al. 2009). Humanized mice are primarily used to solve crucial issues that are extremely difficult or impossible to study on humans. The downside for the patient is that the disease process can only be studied after T1D is clearly defined, and humanized mice can be engineered to identify the factors that lead to the disease. Humanized mice are exceptional in that they can not only recruit immune cells from peripheral tissues, but also receive immune cells from the target organ (pancreas), so that these immune effector cell populations can be investigated. They can also enable the detection of potential treatment goals and the testing of new treatments *in vivo* without affecting the patient (Greiner et al. 2011).

3. Tolerogenic dendritic cells

Tolerogenic DCs (tolDCs) are dendritic cells with a stable, partially mature phenotype and tolerogenic properties. A specific subpopulation of DCs with tolerogenic activity (DC-10) has been detected *in vivo* in peripheral blood and spleen in humans (Comi et al. 2020). Furthermore, DCs can obtain a tolerogenic phenotype *in vivo* and *in vitro* in reaction to different stimulants including interleukin (IL)-10, transforming growth factor (TGF)-β, vitamin D3, corticosteroids or rapamycin (Morante-Palacios et al. 2020). Tolerogenic dendritic cells are a specific and distinct subset of dendritic cells characterized by their involvement in the induction and preservation of immunological tolerance through several different mechanisms (Sallusto et al. 2002; Maggi et al. 2015). The classification and roles of single cells have been broadened and expanded by recent studies. This occurs through the induction of T cell clonal deletion, T cell anergy (functional attenuation), and the formation and activation of regulatory T cells (Hilkens et al. 2013; Bell et al. 2017; Domogalla et al. 2017).

Immunosuppressive processes of tolerogenic DCs include production of immunomodulatory agents, such as TGF-β and interleukin (IL)-10 or retinoic acid, leading to the induction of tolerogenic DCs, suppression of effector T cell activity, and generation of Tregs (Iwata et al. 2004).

Among other features, tolDCs have the potential to induce T-regulatory and B-regulatory cells and the production of anti-inflammatory cytokines. Tolerogenic dendritic cells can suppress immune responses in both antigen independent and antigen-specific manner, i tis however their disposition to induce antigen-specific tolerance, that has to led to their intense research as a promising specific therapeutic tools for the treatment of autoimmune diseases and other immunopathological conditions without the adverse effects of general immunosuppression (Grohová et al. 2017). Usual immunosuppressive treatment is not targeted specifically to this disease and is associated with severe side effects. Tolerogenic DCs have the advantage that they are potent central regulators of immune responses at several checkpoints and can be generated *ex vivo* in sufficient numbers. They could be used unspecifically, without risk of autoantigen burden, by a more attractive specific therapeutic strategy to induce, enhance or restore (antigen-specific) resistence (Stojanovic et al. 2017).

One of the main advantages of tolerogenic DC vaccination is their potential to act in an antigen-specific way (Garcia-Gonzales et al. 2016; Moreau et al. 2017). In general, tolerogenic DCs with uniquely different immunomodulatory actions can be induced in vitro by various

routes that involve genetic engineering, exposure to immunomodulatory pharmacological agents, or the addition of various cytokines and growth factors (Morelli et al. 2007).

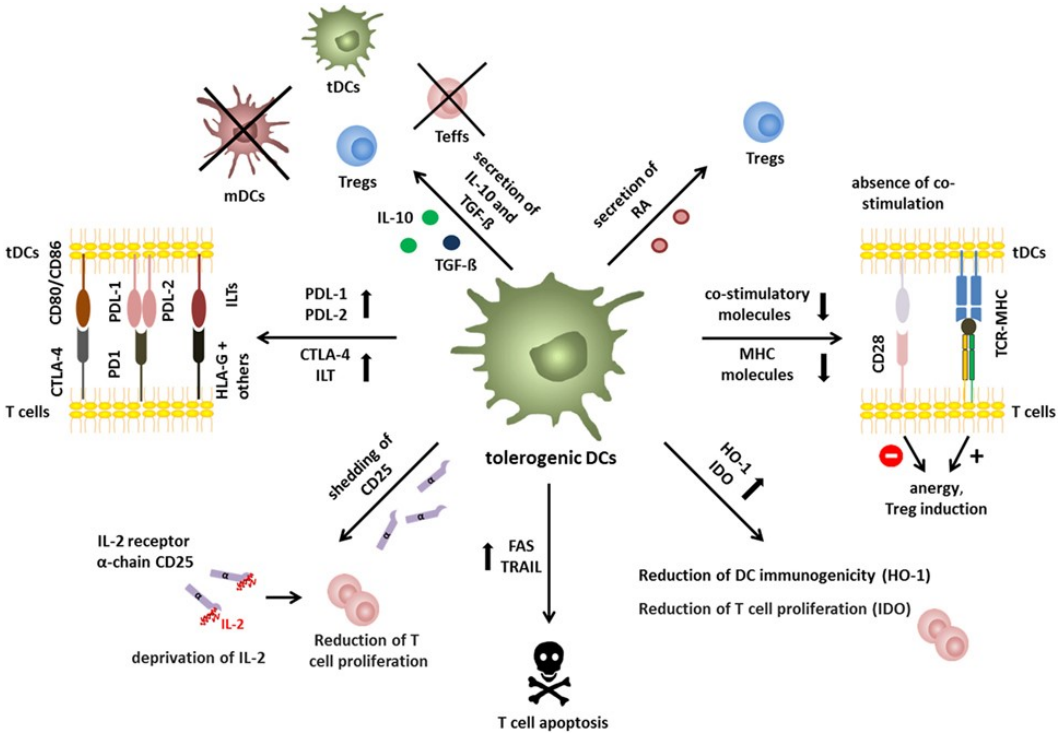

Figure 2. Immunosuppressive mechanisms of tolerogenic dendritic cells (DC). Mechanisms of tolerogenic DCs consist of production of immunomodulatory mediators such as TGF-β, interleukin (IL)-10 or retinoic acid, leading to induction of tolerogenic DCs, suppressing effector T-cell function and Treg production. In addition, the lack or reduction of major histocompatibility and co-stimulatory molecules is involved in the induction of anergic T cells with regulatory capacity. The expression of immunomodulatory/inhibitory molecules such as PDL-1/-2, CTLA-4 and ILT-3/4, or the expression of death receptors such as TRAIL or FAS, are mechanisms of inhibition of effective T cell responses by tolerogenic DCs. In addition, suppression of nutritional factors by expression of indoleamine 2,3-dioxygenase (IDO) and heme oxygenase-1 (HO-1) leads to reduction of T cell proliferation and induction of Treg. Similarly, secretion of soluble CD25 leads to IL-2 deprivation and reduced T cell proliferation (Reprinted and edited from Domogalla 2017).

3.1. Tolerogenic dendritic cells as immune interventions in prevention of T1D

Tolerogenic dendritic cells being investigated as unspecific or specific immunotherapies for their possible application in the treatment of inflammatory, autoimmune and allergic diseases and in transplantation medicine for the prevention of graft rejection (Hilkens et al. 2013). In this context, a thorough knowledge of the mechanisms by which tolDCs induce tolerance is essential for evaluating the properties and potential clinical use of various tolDCs derived *in*

vitro (Jenkins et al. 1987; Ten Brinke et al. 2015). In autoimmune diseases, clinical intervention trials have been tested or are being undertaken for diseases such as type 1 diabetes, rheumatoid arthritis, multiple sclerosis or IBD - Crohn`s disease (Phillips et al. 2017). In type 1 diabetes clinical trials with both antigen unspecific and autoantigen-specific tolDCs have started (Giannoukakis et al. 2011).

3.2. Phenotype properties of tolDCs

Tolerogenic DCs possess a variety of phenotypic features, yet they are generally characterized by low surface expression of costimulatory molecules (CD80, CD83, and CD40; CD, cluster of differentiation). These molecules are important for the activation of effector T lymphocytes (Steinman et al. 2003). On the other hand, they expose inhibitory surface molecules PDL-1, 2 (programmed cell death ligand) , which interact with receptors on T-lymphocytes and cause their apoptosis or anergy (Freeman 2000; Wu et al. 2009; Latchman et al. 2001). Anergy is generally a non-responsive condition that keeps T-cells in a shut down state in circumstances where immune response is undesirable. This mechanism is used to prevent autoimmunity, in the context of controlling T cell responses against self antigen (Maggi et al. 2015). They also exhibit regulatory molecules such as ILT-2, 3, 4 (immunoglobulin-like transcript). In addition, tolerogenic DCs have an appropriate cytokine profile that contributes to their regulatory potential (Osorio et al. 2015).

Tolerogenic DCs produce little or no amount of the inflammatory cytokine IL-12, which is a major stimulus for T-lymphocyte activation and proliferation. They are also characterized by production of anti-inflammatory cytokines such as IL-10 or transforming growth factor-beta (TGF-β), leading to attenuation of T cell proliferation and induction of regulatory T lymphocytes (Steinman et al. 2003; Roncarolo et al. 2007; Steinman 2003). TGF-β-induced DCs exhibit tolerogenic character and function. Supplementation of these TGF-β-treated tolDCs to transplanted islets resulted in engraftment survival in mice recipients with autoimmune diabetes (Ríos-Ríos et al. 2021). TolDCs exhibit an immature phenotype defined by reduced or absent expression of the stimulating signal along with expression of inhibitory molecules and anti-inflammatory cytokines. They can present antigen to T-lymphocytes and thus initiate TCR modulation, and then activation signal 1 is generated.

However, the immature tolDC-related phenotype is defined by reduced levels of costimulatory molecules such as CD80 , CD83 and CD40 (activation signal 2), with low or no

expression of pro-inflammatory cytokines (activation signal 3).These characteristics of tolDC support T cell anergy and/or differentiation of Tregs (Gabrilovich et al. 2004).

3.3. Mechanisms of induction and function of tolerogenic DCs

The mechanisms of tumor escape have been observed for a long time, and upon analysis, cancer cells and the associated stroma have been found to convert myeloid DCs in the tumor microenvironment into tolerogenic phenotypes and to activate regulatory immune responses by various mechanisms including Tregs to achive subsequent suppression of antitumor immunity. (Gabrilovich et al. 2004; Ghiringhelli et al. 2005). The tolerogenic and regulatory DC complex is heterogeneous and can therefore be separated into naturally appearing regulatory DCs and induced tolerogenic DCs (Gordon et al. 2014). Thymic DCs present their own antigen to thymocytes (thymus maturing lymphocyte) and thus subscribe to the induction of central tolerance. They exhibit a tolerogenic phenotype and function because they are influenced by thymic stromal lymphopoietin (TSLP) (Oh 2015). DCs are found in all tissues, but only in certain tissues do they exhibit a tolerogenic character under steady-state conditions. This includes, for example, myeloid DCs or pulmonary plasmacytoid DCs. Immature DCs (iDCs) show low immunogenicity due to lower surface expression of costimulatory molecules and moderate levels of MHCII. Thus, they can be termed tolerance inducers under steady-state conditions. Naive T cells can be transformed to Tregs by repeated stimulation with human iDCs. (Levings et al. 2005, Jonuleit et al. 2000).

3.4. Induced tolerogenic DCs in humans

Immature DCs are located in the peripheral tissues and have a phagocytic character that allows them to take antigen samples from the surrounding area. They achieve their migratory phenotype by activating pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) (Liu et al. 2015).

In contrast to DC migrating from parenchymal organs and resident lymphoid tissue DC, many DC are at risk of immunogenic maturation depending on environmental factors present in the crevasses, airways, and skin. However, these DCs do not induce adverse immune reactions and instead evoke tolerogenic properties. Specific tolerogenic mechanisms are characterized by increased secretion of anti-inflammatory cytokines and additional regulatory molecules (Courtney et al. 2020).

3.5. Antigen-specific vs. unspecific approaches

The main principle of the use of tolDCs is based on the idea that enhancement of the tolerogenic component of the immune system would renew immune homeostasis and handle the disease (L. Passerini, S.Gregori, 2021). Both unloaded tolDCs and antigen-specifc tolDCs are being tested in autoimmune diseases (Stojanovic et al. 2017; Phillips et al. 2017; Funda et al. 2019). As regards the use of unloaded tolDCs, in addition to being safer than antigen specific tolDCs approach, they were, when tested in animal models, surprisingly equally or even more effective in disease prevention (Machen et al. 2004, Ma et al. 2003; Funda et al. 2018).

Antigen-specific approaches for autoimmune disease have to be preceded by a proper consideration of the situation, because of the introduction of a specific antigen into an already activated, proinflammatory and non-tolerogenic environment-thus it may represent a substantial risk also to augument the already estabilished autoimmune respons. Several parameters such as are the correct choice of antigen, the route and frequency of application should be considered, but the stability of tolDCs is the key safety issue in this therapeutical approach (Naranjo-Gómez et al. 2011; Smyth et al. 2013). A number of antigens found in pancreatic islets have been identified among the best researched are (pro-)insulin, glutamic acid decarboxylase 65 (GAD65) and tyrosine phosphatase-like protein ICA152 (IA-2). Several studies tested autoantigen loaded tolDCs in T1D animal models researching their mechanisms and confirming their safety and efficacy (Haase et al. 2010; Lo et al. 2006; Marin-Gallen et al. 2010).

New perspectives in relation to T1D have been opened by the identification of neoepitopes. These comprise peptides with improved MHC linkage registers, such as the insulin peptide InsB 9-23 with combined replacements at positions 14, 21 and 22, peptides generated by peptide fusion, such as aberrant translation or hybrid insulin peptides (HIPs), such as the INS-DriP peptide. Recent studies have shown that they induce robust T-cell-specific reactions. These profoundly immunogenic peptides displayed by tolDC are promising devices to reconstruct pathogenic T cells and actuate resilience in T1D (L. Passerini, S.Gregori, 2020).

3.6. Therapeutic applications and migration of TolDCs

Myeloid suppressor cells (MSCs), Tregs and tolDCs express several target receptors that are essential for their trafficking from the injected tissue (e.g. skin or blood vessels) to sites of activation (e.g. regional lymph nodes) and finally to the target organs (Huehn et al. 2005). Activated tolDCs express CCR7 and then migrate to CC chemokine ligand 19 (CCL19) (Anderson et al. 2009), which underpins migration to regional lymph nodes. Clearly, it is important to consider migration potential when designing cell therapies (Sordi et al 2005).

Several application pathways of tolDCs have been used in humans. In addition to intradermal administration in patients with T1D (Giannoukakis et al. 2011) and rheumatoid arthritis (Benham et al. 2015), tolDCs have been injected intraperitoneally in patients with Crohn's disease (Jauregui-Amezaga et al. 2014), subcutaneously and arthroscopically into the joint in patients with inflammatory arthritis. (Joo et al. 2014). No toxic effect has been noted in any of these routes of administration (Ezzelarab et al. 2017).

In 2001, Ralph Steinman's group performed the first experiment on the application of tolDCs to humans (Dhodapkar et al. 2001, 2002). It was found that subcutaneous administration of human immature tolDCs, at a dose of $2x10^6$, into healthy subjects suppressed antigen-specific CD8+ T cell responses and was tolerated for up to 6 months. These tolDCs, were generated in the vicinity of granulocyte and macrophage colony-stimulating factor (GM-CSF) and IL-4 and pulsed with antigens and have become a significant indicator of tolerogenic potential in humans in vivo (Jauregui-Amezaga et al. 2014).

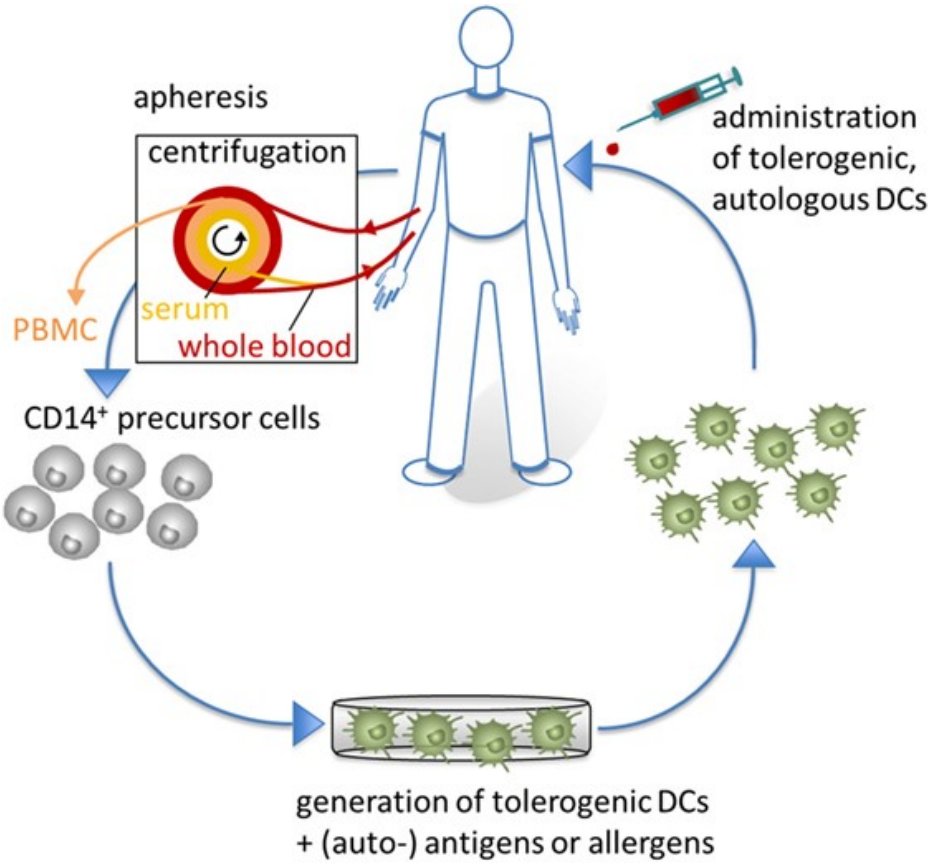

Figure 3. TolDCs in clinical use. CD14+ monocytes are separated from apheresis products for clinical applications to create tolDCs that are expressing allergens or autoantigens. They are then re-injected into recipients to influence the abnormal immune response in autoimmune or allergic diseases. (Reprinted and modified from *Domogalla et al. 2017*).

3.7. Generation of tolerogenic dendritic cells

Human tolDCs are generated from peripheral blood monocytes whereas in animal models and experiments tolDCs are propagated from bone marrow precursors. Precursors are separated by cell sorter, microbeads, or elution (Moreau et al. 2017). The initiation of tolDC production occurs by exposing cells to growth factors like the GM-CSF and cytokines such as IL-4, which are used to differentiate precursors into immature DCs. The immunomodulatory substances IL-10 or TGF-β, which are cytokines with anti-inflammatory effects, or pharmacological agents rapamycin, vitamin D3, vitamin D2 and dexamethasone, which induce the acquisition of tolerogenic properties, are also involved in the process (Ríos-Ríos et al. 2021). The active form of vitamin D (vitD3, 1,25(OH)2D3) seems to be a powerful immunomodulatory factor for tolDCs in connection with their impact on T cells. DCs seeded with VitD3 back antigen-specific administrative T cells, coming about in irresistible resistance through the re-education of pro-inflammatory develop DCs into DCs with administrative highlights of Tregs (Kleijwegt et al.

2011). In addition, they block T cell activation and persuade apoptosis of effector T cells. (Nikolic & Roep 2013).

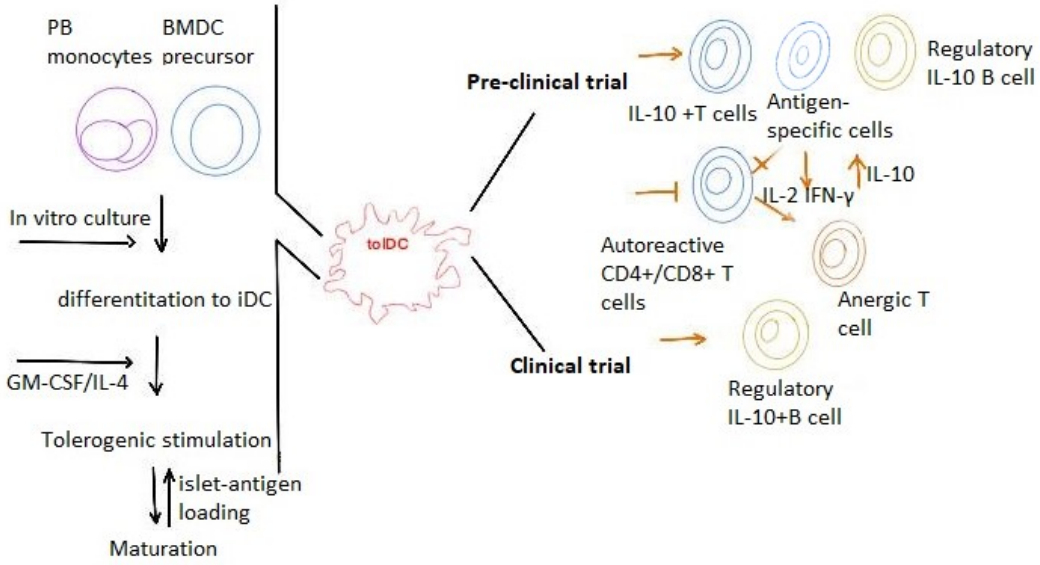

Figure 4. Tolerogenic dendritic cells in the treatment of type 1 diabetes: described production and mechanisms in preclinical and clinical studies. In humans, tolDC are produced from peripheral blood monocytes and in mice from bone marrow precursors that are affected by sequential stimulation in in vitro culture. First, immature DC are formed and generated by growth factors, which are treated with immunomodulatory drogs for the purpose of acquiring a tolerogenic character. To achieve stable tolDCs, they interact with other stimulatory agents, for example lipopolysaccharide or tumor necrosis factor, in the recent or following a tolerogenic pulse. TolDCs can elicit an enhanced population of cells expressing IL-10 and augment the population of antigen-specific regulatory T cells that exhibit optimal suppressive activity; tolDCs further inhibit the initiation and engraftment of autoreactive naive and storage CD4+ and CD8+ T cells, otherwise they become anergic. In addition, the regulatory functions of tolDCs also extend B cells, because high levels of IL-10-expressing regulatory B cells are expanded by tolDCs, which are associated with a protective role for T1D.

BMDC: bone marrow-derived dendritic cell; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN: interferon; PGEs, which have been connected with a protective function in type 1 diabetes and are the only reported immunoregulatory mechanism derived from a clinical study. BMDC: bone marrow-derived dendritic cell; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN: interferon; PGE2 : Prostaglandin E 2 ; PB: peripheral blood; IL: interleukin; tolDC: tolerogenic dendritic

cell; TGF: transforming growth factor; LPS: lipopolysacharide *(Reprinted and modified from Ríos-Ríos, 2021).*

3.8. Disadvantages of tolDCs

Diagnostic imaging studies in animals revealed important details of the natural migration of tolDcs (Creusot et al. 2009). Simultaneous progress in cell manufacturing technologies promises scalability, if safety and effectiveness can be proven. These cell therapies include tolDCs and regulatory T cells (Tregs). Each approach has its benefits and drawbacks, especially in terms of demand for treatments customized to specific patient needs versus "off-the-shelf" treatments, but also in terms of their usefulness in specific clinical situations (Mosanya 2019). The main disadvantage of both tolDCs and Tregs as *ex vivo* cell therapies is the requirement for extensive in vitro manipulations or their costly and laborious preparation adapted to patient requirements (Funda et al. 2019).

3.9. Treg cells and their therapeutic induction

A characteristic feature of diabetes is hyperglycemia, which has several negative effects on the immune system. It affects APC function, contributes to the breakdown of peripheral tolerance, simplify the differentiation of Th1/Th17 pro-survival cells and suppresses the function of regulatory T cells (Tregs) (Dáňová et al. 2017). Recent studies have been directed at studying the biology and physiology of Tregs and their mechanisms of attack. Non-clinical trials have shown the potential of Tregs to delay/inhibit transplant rejection and check autoimmune responses after adoptive transfer *in vivo*. With these prospective findings, Tregs continue to be investigated as a potentially useful new therapeutic agent for protection against transplant rejection or for the treatment of autoimmune diseases (Romano et al. 2019; Trzonkowski et al. 2015).

Tregs are essential for the maintenance of tolerance and are seen in equal numbers in healthy and diabetic patients, but show decreased regulatory potential in patients, which may affect the pathogenesis of T1D (Lindley et al. 2015).

Tregs are specifically used to regulate the autoimmune response and are therefore essential for maintaining immune system homeostasis (Suwandi & Laban 2020). The best described subset is Forkhead box P3 expressing Tregs (FOXP3+ Tregs) (Romano et al. 2019) and IL-10 regulatory type 1 (Tr1) cells (Passerini & Gregory 2020).

Tregs that robustly express the transcription factor Foxp3 (Foxp3+ Tregs) suppress the progression of autoimmune diabetes in NOD mice, and compelling evidence exists that they may control the supplies of autoreactive CD4+ and CD8+ effector T cells in humans (Phillips & Garciafigueroa 2021). However, in type 1 diabetes, lack of tolerance to beta cell antigens leads to wrecking of insulin-producing cells. Strategies to induce or enhance the number of Tregs, leading to reduced immune inflammation in humans with autoimmune diseases, have been widely used (Suwandi & Laban 2020).

3.10. The route of administration

Significant *ex vivo* accumulation of expanded DCs in the PLN of mice was observed after i.v. (intravenosus) or i.p. (intraperitoneal) injections. TolDCs injected s.c. (subcutaneously) into the respective abdominal regions in mice can also reside in PLNs (pancreatic lymph nodes) (N.G. and M.T., unpublished observations).

Systemic administration by intravenous injection provides the opportunity to reach other secondary lymphoid tissues, such as the spleen, which can also be important for inducing tolerance. Therefore, studying combinations of multiple pathways may be advantageous, for any treatment, to broaden the reach of tolDCs. Despite the fact that seldom i.p., and no omental or paragastric intranodal injections are routinely performed in humans, they seem to be the most effective for targeting PLNs, at least in mice (Creusot et al. 2014).

The next step in this direction would be larger studies on non-human primates or analysis of surgically removed PLN or laparoscopically from patients after intraperitoneal, intravenous or subcutaneous DC injection in existing models of cancer therapy (Creusot et al. 2014).

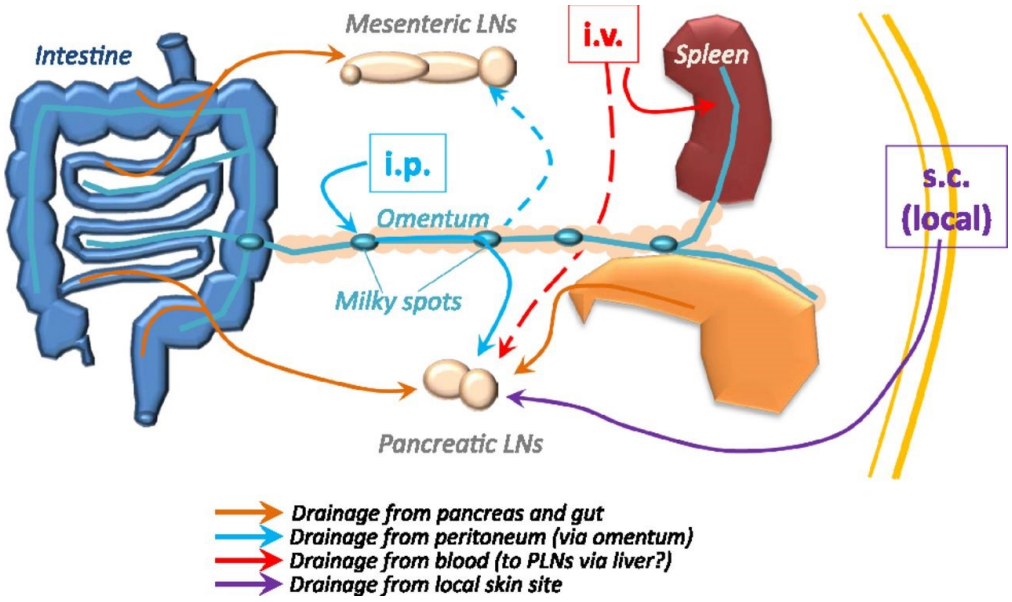

Figure 5. PLN as a central station for DC. Studies in mice have revealed the remarkable centrality of PLN in the immune system. Not only the pancreas but also the intestine and peritoneum proved very effective. After i.v. and i.p. application, DCs primarily accumulate in PLNs, despite the fact that the mechanism is not fully explained. In addition, after s.c. injection in the abdominal landscape, targeting of DCs to PLNs also occurs. The pathways in humans are not quite as well developed and are probably more complicated. Combining specific pathways under the action of integrin and chemokine receptors leads to more targeted and effective tolerance-inducing therapy (Reprinted and modified from Creusot, 2014).

3.11. Number of administrated cells and their antigen specificity

There are major development issues, like dosage and administration frequency- treatment with tolDCs should only require one cycle of therapy, but in a patient with a tendency for autoimmunity, regular repeat administration is likely to be necessary to keep autoreactivity at optimal levels (Mosanya & Isaacs 2019).

TolDC therapy normally consists of 0.5-5 × 106 cells injected either in a single dose or in multiple injections at one-week intervals, and in an initial human T1D study, DCs were administered four times, once every two weeks (Giannoukakis et al. 2011). Serious adverse effects were not observed even when large numbers of cells were injected.

4. Perspectives and future view at T1D therapy

In the past decades, β-cells have not been sufficiently studied and were considered "victims" of this autoimmune attack. As a result, interventional therapies have focused only on inhibiting the adaptive immune system but have shown limited success. Research has shifted towards the target tissue of the β-cells provoking autoimmunity and there is growing evidence that β-cells are at the centre of the pathogenesis of T1D initiation. The stressed β-cells have been proven to initiate an autoimmune response in a pre-disposing genetic and immunological environment (Zirpel & Roep 2021). The assumption that T1D is a disease of the adaptive immune system has been disproven in the recent decade (Roep et al. 2020). Several observations point to other key contributors.

β-cells are specialized to deliver high amounts of insulin. This ability is impaired by a decrease in defence mechanisms and a considerable vulnerability to stress. Cells need insulin for their existence, and therefore cellular stress increases in the absence of insulin. A smaller pancreas means a reduced number of β-cells, which in turn increases the metabolic pressure on the islets. Several other factors have been proposed as stressors, such as viral infections or inflammatory environments. Stress markers located in the endoplasmic reticulum, such as CHOP, BIP and XBP-1, pointed to the fact that pancreata from T1D donors exhibited elevated intracellular β-cell stress during insulitis. Stress to β-cells can evoke adaptive immunity, but this necessitates the participation of the intrinsic immune system, because once triggered by dendritic cells, islet auto-reactive T-cells are initiated by the stimulation of islet immunogenic molecular peptides. Stressors released from ß-cells indicate that T1D affects the adaptive immune system as well as ß-cells, where disrupted ß-cells switch their identities and form the immune system (Zirpel & Roep 2021).

T1D is a controlled disease that requires treatment. Despite investment in new insulin preparations and blood glucose-activated pumps, pharmacological insulin replacement therapy will not restore stable and long-term physiological blood glucose variability to prevent complications (Phillips, et al. 2019). The results of human clinical trials to date have shown that cell therapies are at least safe, precise and workable, and therefore worth further exploration in the efforts to induce therapeutic tolerance (Mosanya et al. 2019).

We can note with confidence that the detection rate of autoimmunity and the prediction of T1D risk have improved significantly. The development of T1D can be recognized by islet-

specific autoantibodies and biomarkers, including circulating insulin DNA (Eitan M. Akirav, et al., 2011) or miR-375 (S. Erener, M. Mojibian, 2013).

Autoantibodies directed against beta cell proteins and peptides, although not directly involved in the disease pathogenesis, are now recognized as presymptomatic biomarkers for early diagnosis of T1D. Currently, autoantibodies targeting insulin, glutamic acid decarboxylase, tyrosine phosphatase-like protein, and zinc transporter-8 (ZnT8) are mainly applied as biomarkers of type 1 diabetes in the clinics (Mathieu & Lahesmaa 2018). Autoantibodies in genetically predisposed subjects can be discovered in the blood several years before the clinical appearance of the disease (Bluestone et al. 2021; Bach 2021).

5. Conclusion

Based on available research, there is still no effective preventive strategy that would target autoimmune pathways that underlies T1D in humans. In the context of already manifested diabetes, no effective cure, either as a single or combination therapy, is available at present, although several promising results have been gained in animal models of T1D.

Tolerogenic DC (tolDC) vaccination as an alternative immunotherapy may represent an effective therapy for autoimmune diseases including T1D. TolDCs have been shown to improve the course of disease because of their ability to reduce the hyperactivity of effector immune cells in both antigen unspecific and antigen-specific manners. The NOD mouse continues to be an extraordinary model because it spontaneously develops T1D and similar to human T1D is sensitive to environmental factors, that are substantially influencing the development and incidence of T1D worldwide.

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