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Type 1 diabetes – What's new in prevention and therapeutic strategies?

Cukrzyca typu 1 – co nowego w profilaktyce i terapii?

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Abstract

Type 1 diabetes (T1D) is an autoimmune disorder, and insulin deficiency is the result of β-cell dysfunction. Treatment of type 1 diabetes requires constant parenteral insulin administration, which can be very burdensome for the patient. Meticulous use of insulin therapy does not protect the patient against complications. Hence, the search for other methods of treatment as well as ways of preventing the onset of diabetes has been ongoing for a long time. The main obstacle in the implementation of the prevention task is the need to identify people at risk of developing diabetes before the start of autoimmunity. It seems that primary prevention is still unrealistic at the moment, because we do not know all the factors leading to the activation of autoimmunity processes. Research on the use of late secondary prevention in people who develop glucose tolerance disorders or in the early period after the onset of type 1 diabetes are at the most advanced stage. Gene therapy is another attempt at an alternative treatment and prevention of type 1 diabetes and still requires further research. Recent years have brought a lot of information about the nature of type 1 diabetes and the mechanisms leading to its development. However, it has not yet been established what factors decide about the initiation of autoimmunity and what determines the dynamics of these processes.

Key words: gene therapy, type 1 diabetes, prevention of type 1 diabetes, pancreas transplants.

Streszczenie

Cukrzyca typu 1 jest chorobą autoimmunologiczną, a niedobór insuliny jest wynikiem dysfunkcji komórek β. Leczenie cukrzycy typu 1 wymaga stałego podawania insuliny, co może być bardzo uciążliwe dla chorego. Bardzo skrupulatne stosowanie insulinoterapii nie chroni pacjenta przed powikłaniami. Dlatego od dawna trwają poszukiwania innych metod leczenia, a także sposobów zapobiegania zachorowaniu na cukrzycę. Główną przeszkodą w realizacji zadania profilaktycznego jest konieczność identyfikacji osób zagrożonych zachorowaniem na cukrzycę przed wystąpieniem autoimmunizacji. Wydaje się, że w chwili obecnej profilaktyka pierwotna jest nadal nierealna, ponieważ nie znamy wszystkich czynników prowadzących do aktywacji procesów autoimmunologicznych. Najbardziej zaawansowane są badania nad zastosowaniem późnej profilaktyki wtórnej u osób, u których rozwijają się zaburzenia tolerancji glukozy lub we wczesnym okresie po zachorowaniu na cukrzycę typu 1. Terapia genowa jest kolejną próbą alternatywnego leczenia i profilaktyki cukrzycy typu 1 i nadal wymaga dalszych badań. Ostatnie lata przyniosły wiele informacji na temat natury cukrzycy typu 1 i mechanizmów prowadzących do jej rozwoju. Nie ustalono jednak jeszcze, jakie czynniki decydują o inicjacji autoimmunizacji i co determinuje dynamikę tych procesów.

Słowa kluczowe: cukrzyca typu 1, profilaktyka cukrzycy typu 1, terapia genowa, przeszczep trzustki.

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder, and insulin deficiency is the result of β-cell dysfunction. In type 1 diabetes, cells are destroyed by autoimmune processes that are related to genetic predisposition and the action of environmental factors. The genetic predisposition of the organism is related to the HLA gene complex located on the shorter arm of the 6p21 chromosome (IDDM1). The main role of allelic variation of the HLA-DRB1, HLA-DQA1, and HLA-DQB1 class II *loci* has been established [1]. Analysis of the entire human genome using a mapping technique identified other sites associated with type 1 diabetes. Regulatory lymphocytes (Treg) play a role in controlling immune responses; however, despite many research programs, it has not been possible to establish the mechanisms responsible for losing immune control over these lymphocytes. Treatment of type 1 diabetes requires constant parenteral insulin administration, which can be very burdensome for the patient. Moreover, even very careful use of insulin therapy does not protect the patient against complications.

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Hence, the search for other methods of treatment as well as ways of preventing the onset of diabetes has been going on for a long time. Several international programs were conducted to establish risk indicators for diabetes. These studies concerned both genetic and environmental indicators. An extensive review of the research on the mechanisms leading to the development of diabetes was recently presented by Klak *et al.* [2]. The sequence of processes leading to the eventual destruction of β cells is not definitively clear. Among the factors responsible for activating the processes of autoimmunity, dietary factors, viral infections, etc. were taken into account [3–6]. A review of the research on the mechanisms of β-cell death in diabetes was recently presented by Mukherjee *et al.* [7]. Autoantibodies appearing in type 1 diabetes are believed to be humoral indicators of β-cell destruction. Several β-cell antigens that can stimulate antibody production are already known, but it is worth emphasizing that there is a group of type 1 diabetes mellitus in which no autoantibodies are found. During the development of type 1 diabetes, several phases can be distinguished, in which the presence of various markers of the ongoing disease process is characteristic. The dynamics of these changes can be very different, which determines the period of clinical manifestation of diabetes. The first phase is the period of the genetic predisposition of the organism. The diagnosis of this period may be based on genetic tests. The genetic risk score (GRS) for type 1 diabetes is now available to facilitate the integration of complex genetic information, disease prognosis and prediction, and response to preventive and therapeutic interventions [8]. The second phase is the period when, as a result of various factors, the process of β-cell destruction begins in the body. It is manifested by the appearance of autoantibodies directed against the antigens of these cells. It is assumed that infectious agents, mainly viruses, nutrients, and various toxic substances, may be the "triggers" of these destruction processes. Destruction of approximately 90% of the β cells leads to clinically manifest diabetes. A discussion of the research on this issue was recently presented by Wong and Tree [9, 10]. In their article, they presented a set of 4 review articles that cover new findings presented at the 2018 Immunology of Diabetes Society meeting in London [9]. In the second paper, they presented further insights into the generation of post-translationally modified peptides [10]. Quinn *et al.* in their review presented the evidence to date supporting pathways from relationship to causation in all stages of type 1 diabetes (seroconversion to β cell failure) [11].

Prevention of type 1 diabetes

Simultaneously with the search for methods of better and better treatment of type 1 diabetes, work is underway on methods to prevent its occurrence [12–14]. In the context of type 1 diabetes prevention, we can divide the activities into primary prevention, i.e. prevention of autoimmunity, and secondary prevention, i.e. prevention of overt hyperglycaemia in people with established autoimmunity and intervention studies aimed at preserving C-peptide [12]. We also distinguish tertiary prevention, which focuses on the complications of the disease, and its main goal is to delay their occurrence [15]. Primary prevention conducted in the period when the process of autoaggression against β cells has not yet started consists of the modification of risk factors that predispose their activation. The main obstacle in the implementation of this task is the need to identify people at risk of developing diabetes before the start of autoimmunity. It turned out to be difficult due to the low specificity of the genotypes. The increasing incidence of type 1 diabetes suggests that unknown environmental factors play a role in its pathogenesis. Abel and Fav's study of prenatal and early life factors suggests that factors influencing the skin or gut microbiome may play a greater role than infections and factors influencing the microbiome in other places [16]. Research on the influence of the microbiome on DM1 development may provide insight into the development of safe strategies for modulating immune regulation in infants and children. Kordonouri *et al.* showed that certain bacterial infections may increase the risk of autoantibodies and the development of type 1 diabetes. In that study poor support was shown for viral infections [17]. Caramalho *et al.* in their study showed that bacterial product lipopolysaccharide (LPS) promotes the expansion and enhances the function of disease-preventive Treg [18]. In turn, Filipi *et al.* indicated that TLR2 stimulation in a naive context or after viral infection conferred protection against autoimmune diabetes [19]. The potential role of infection in the pathogenesis of DM1 has resulted in the development of research on vaccination, not only against viruses but also on vaccines inducing immune tolerance to beta-cell antigens [20–22]. Results from Hoyne *et al.* revealed a role for peripheral T cell anergy in organ-specific self-tolerance [23]. On the other hand, Hortani *et al.* in their study showed that mesenchymal stem cell (MSC) therapy can prevent the incidence of diabetes associated with immune checkpoint cancer therapy and may be worth further consideration for new adjuvant cell therapy [24]. Moreover, dendritic cells were checked as a therapeutic alternative in the treatment of type 1 diabetes [25]. Clinical trials are also undertaken, but for now, they are scientific research [26–29]. Secondary prevention concerns the preclinical period, and possibly the period immediately after the onset of the disease [30, 31]. Recently, an extensive discussion of this issue was presented by Toren *et al.* [32]. They underlined in their research β-cell vulnerability, heterogeneity, and contributions to the pathophysiology of T1DM and described pathways that can potentially be exploited to delay T1DM [32]. The evaluation of the results of experimental studies is difficult due to the differences between human antibodies and those of experimental animals; hence, there are attempts to develop a new model of humanized mice to conduct research on the use of immunotherapy in the treatment of type 1 diabetes [33]. Research on the use of late secondary prevention in people who develop glucose tolerance disorders or in the early period after the onset of type 1 diabetes is at the most advanced stage. Promising results of secondary prevention of type 1 diabetes are related to the use of stimulated immunomodulation in newly diagnosed type 1 diabetes [34]. Marek-Trzonkowska *et al.* presented the results of research on obtaining regulatory T cells from conven-

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tional T lymphocytes isolated from peripheral blood in children with type 1 diabetes. At the same time, changes in the expression of selected genes important for the functions of these cells during the generation of Tregs were assessed [35]. The authors showed that the administration of Tregs is safe and tolerable in children with recent-onset type 1 diabetes. Attempts are being made in experimental studies to use the suppressor effect of myeloid-derived suppressor cells (MDSCs) to inhibit the immune response [36, 37]. Myeloid-derived suppressor cells are a heterogeneous population of immature cells with immunosuppressive abilities. Recently, there have been many reports on the use of antibodies (anti-CD3 antibodies like teplizumab or otelixizumab) in the prevention of the development of type 1 diabetes [38, 39]. There are also numerous attempts by bioengineered β cells to stimulate the growth and differentiation of β cells and inhibit apoptosis processes [40–43].

Gene therapy

Gene therapy is another attempt at an alternative treatment and prevention of type 1 diabetes. Studies on this therapy are performed in animal models; therefore, safety in humans has not yet been established. Work on this therapy consists of overexpression of genes and proteins needed against T1DM, transplantation of cells that express the gene against T1DM, stem cell-mediated gene therapy, genetic vaccination, immune precursor cells, gene therapy, and vectors [44]. Chellappan *et al.* in their review discuss the essential genes and proteins that can be overexpressed for the treatment of DM1 through gene therapy [44]. Cell transplants expressing genes against T1DM and genetic vaccinations have been reviewed, which also show promise in the treatment of T1DM. Moreover, immunological interventions using gene therapy have been described, which are also potentially therapeutic approaches for T1DM. Several viral and non-viral vector systems are also discussed, with each system having its own advantages and limitations [44]. The main problem is finding methods for the safe transfer of therapeutic genes into cells [45]. Gene therapy still requires further research.

Treatment of type 1 diabetes

Insulin

From its discovery (100 years ago) to the present day, insulin has remained the mainstay of treatment for type 1 diabetes. However, exogenous insulin is still not able to completely mimic the physiological insulin secretion profile. Therefore, concepts based on its administration via the oral or inhalation route are emerging [46]. Khan *et al.* in their systematic review found that inhaled insulin is as effective as subcutaneous insulin in patients with type 1 diabetes. Inhaled insulin resulted in less weight gain, fewer episodes of hypoglycaemia were observed, and there was no significant difference in the incidence of adverse events. On the other hand, it has a very short duration of action, so it should not be used alone, but in this case with other basal insulins [47].

Pancreas transplants

Pancreas transplantation is the oldest alternative treatment for diabetes. Transplants began in the 1960s and were performed mainly in patients with diabetes and end-stage renal failure. The pancreas was usually transplanted simultaneously with the kidney. The problem in the development of this method of procedure was not only the difficulty in obtaining a suitable organ for transplantation, and the fact that pancreatic transplantation is relatively technically difficult due to its structure and location, but also due to the need to use aggressive immunosuppression. Immunosuppressive therapy of pancreas transplantation consists of induction with depleting antibodies and maintenance with tacrolimus, mycophenolate, and steroids [48]. The introduction of new procedures of immunosuppressive therapy has significantly improved the effects of transplantation; however, such treatment is still burdened with high risk. An alternative to the difficult and expensive pancreatic transplantation is a much less expensive and simpler method of transplanting isolated pancreatic islets or β cells. The first isolation of pancreatic islets was performed by a Pole, Prof. S. Moskalewski, in 1965 [49]. Treatment of diabetes mellitus should be optimized first in patients being considered for pancreatic transplantation. Pancreatic transplantation can be a form of treatment in patients with irreversible complications of diabetes, such as diabetic nephropathy [50]. It is now a more and more widely used treatment in adult patients (>18 years old) with T1D of 5 or more years and experiencing unrecognized severe hypoglycaemic episodes [51–54]. Human islet isolation and purification require a multi-step process to extract the small islet fraction. Enzymatic digestion, controlled gentle mechanical shear, purification, and culture is the established approach to preparation of a final enriched islet cell product that is considered safe for intra-portal infusion of the recipient's liver [55]. The problem, however, is still obtaining cells for transplantation, as well as their protection against destruction processes after transplantation [56–59]. Recently, an extensive discussion of methods for harvesting cells in animal models has also been presented [60, 61]. The use of both pancreatic and islet transplants is limited due to the small number of deceased donors. Pigs represent one promising renewable source of islets [62]. Clinical attempts to stop the destruction of self β cells by the use of monoclonal antibodies and other factors inhibiting autoimmune processes, as well as blocking immunization processes in relation to transplanted cells, are more and more widely undertaken.

Insulin therapy

The artificial pancreas or automatic insulin delivery system/ closed loop system/ bionic pancreas is a system consisting of 3 parts, which include a continuous glucose monitoring system, an insulin pump, and a program stored on the pump or smartphone. The continuous glucose monitoring system tracks your glucose levels with a subcutaneous sensor. The sensor sends information to a program stored on a smartphone or to an insulin infusion pump. So, this system monitors blood glucose, calculates the amount of insulin needed at different times of the day, and delivers it. Most hybrid systems require

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counting and entering the amount of carbohydrates consumed during a meal [63–65]. Currently, scientists are also working on a dual-hormone system that uses insulin to lower glucose levels and glucagon to raise them. Using 2 hormones to control blood glucose levels is similar to the pancreas in people without diabetes. These systems may be able to closely control glucose levels without causing hypoglycaemia [66].

Immunotherapy

Attention should be paid to the immunotherapy of type 1 diabetes, which is the subject of intensive research. Immunotherapy is designed to keep the disease in a pre-symptomatic stage, preserving residual β-cell function in people with recent-onset type 1 diabetes. Teplizumab, an anti-CD3 antibody, has shown a significant delay in disease progression as an immunomodulatory drug in high-risk individuals before clinical onset [67, 68]. A review of the studies of otelixizumab and teplizumab showed significant benefits in both high-risk T1DM and recent-onset T1DM patients. In high-risk patients, they delayed the time to diagnosis, preserved C-peptide levels, and improved metabolic parameters. Patients with developed diabetes maintained C-peptide levels and reduced insulin requirements for longer periods. This therapy heralds a new era of treatment, seems to be safe, and the side effects are self-limiting and transient [69, 70]. The inhibition of IL-12 differentiation by Th1 cells may be an effective means of inhibiting the development of type 1 diabetes mellitus [71]. A limitation of this therapy is critical Th1 function and side effects. Among the tyrosine kinase inhibitors, sorafenib is the most promising. An animal model showed that sorafenib inhibited the development of type 1 diabetes and may be a promising therapy for type 1 diabetes in humans [71].

Perspectives

Searching for methods of adequate preparation of transplantation of β cells, devoid of immunogenic effects, which would allow abandonment of the use of immunosuppressive drugs.Searching for cells for transplantation from renewable sources, cells capable of both self-renewal and multi-line differentiation. Hopes are also associated with obtaining cells and tissues using the somatic own cells of the transplant recipient, but this method also raises ethical controversies related to cloning methods.

The use of genetic engineering to inhibit the processes of autoimmunity and β-cell apoptosis, both in people at risk of developing diabetes and in patients after islet cell transplantation.

Conclusions

Recent years have brought a lot of research about the nature of type 1 diabetes and the mechanisms leading to its development. However, it has not been established which factors decide the time of initiation of autoimmunity and what determines the dynamics of these processes. Despite enormous advances in glycaemic control thanks to modern insulin therapy methods, no definitive cure for the disease has been found. There are many very different research programs underway, many of which give hope for a final positive solution. For now, however, it must be recognized that type 1 diabetes is still an incurable disease.

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