PREGLED LITERATURE – REVIEW ARTICLE

Association of PTPN22 and Type 1 Diabetes Mellitus

Povezanost PTPN22 i Dijabetes Melitus tip 1

Maja Jović [1], Aleksandar Marković [1], Milica Stanković [2], Tatjana Jevtović Stoimenov [3]

[1] Naučnoistraživački centar za biomedicinu, Medicinski fakultet Univerziteta u Nišu, Srbija
[2] Centar za patologiju i patološku anatomiju UKC Niš, Medicinski fakultet Univerziteta u Nišu, Srbija
[3] Katedra za Biohemiju, Medicinski fakultet Univerzitet u Nišu, Srbija

Summary Diabetes mellitus is a multifactorial metabolic disease and its etiology shows a significant genetic basis. Type 1 diabetes mellitus (T1DM) is most common chronic childhood disease. This autoimmune endocrine disease affects younger people and manifests itself most in puberty. It is characterized by degeneration of β cells of the endocrine pancreas, leading to insulin deficiency. Susceptibility gene polymorphisms in pathogenesis of type 1 diabetes and other autoimmune diseases have attracted a growing amount of attention in recent years. Among them, multiple studies have linked a single nucleotide polymorphism in the gene encoding the protein tyrosine phosphatase non-receptor type 22 (PTPN22) to T1DM. PTPN22 is expressed by many immune cells, such as T and B cells, monocytes, dendritic cells and NK cells. PTPN22 gene encodes lymphoid specific tyrosine phosphatase (LYP), an inhibitor of T cell activation. rs2476601 (R620W, 1858C→T) is one of the most studied LYP variations. This mutation results in partial or complete disruption of PTPN22 CSK (C-terminal Src kinase) binding. The C1858T polymorphism within this gene contributes to the development of T1DM because it reduces the activation of T lymphocytes. Many studies propose this SNP (single nucleotide polymorphism) as a considerable risk factor for T1DM among the Caucasian population. However, this research area shows a lot of potential for development of T1DM preventive treatments and even the prospective chance for application in screening tests, whereas T1DM patients with PTPN22 variant represent a promising target group for prevention trials with highly selective LYP inhibitors.

Keywords: Type 1 diabetes mellitus, PTPN22, polymorphism, children

Sadržaj Dijabetes melitus je multifaktorijalno metaboličko obolenje čija etiologija pokazuje značajnu genetsku osnovu. Dijabetes melitus tipa 1 (T1DM) je najčešća hronična dečja bolest. Ova autoimuna endokrina bolest pogađa mlađe ljude i najviše se manifestuje u pubertetu. Karakteriše je degeneracija β ćelija endokrinog pankreasa, što dovodi do nedostatka insulina. Polimorfizmi gena uključenih u patogenezu dijabetesa tipa 1 i drugih autoimunih bolesti privlače sve veću pažnju istraživača poslednjih godina. Među njima, više studija je utvrdilo povezanost polimorfizma u genu koji kodira protein tirozin fosfatazu-22 (PTPN22) sa T1DM. PTPN22 eksprimiraju mnoge ćelije imunskog sistema, kao što su T i B limfociti, monociti, dendritične ćelije i NK ćelije. PTPN22 gen kodira limfoid tirozin fosfatazu (LYP), koja je inhibitor aktivacije T ćelija. rs2476601 (R620W, 1858C→T) je jedna od najviše proučavanih varijacija LYP. Ova mutacija rezultuje delimičnim ili potpunim prekidom vezivanja PTPN22 za CSK (C-terminalna Src kinaza). C1858T polimorfizam unutar ovog gena doprinosi razvoju T1DM jer smanjuje aktivaciju T limfocita. Mnoge studije predlažu ovaj polimorfizam kao značajan faktor rizika za pojavu T1DM kod belaca. Međutim, ova oblast istraživanja pokazuje veliki potencijal za razvoj preventivnih tretmana za T1DM, pa čak i veliku šansu za primenu u skrining testovima, dok pacijenti sa T1DM varijantom PTPN22 predstavljaju ciljnu grupu za ispitivanje prevencije sa visoko selektivnim inhibitorima LYP.

Ključne reči: Dijabetes melitus tip 1, PTPN22, polimorfizam, deca

Introduction

Diabetes is becoming a severe global public health issue of the twenty-first century, as the prevalence of all forms of diabetes rises. Type 1 diabetes mellitus (T1DM) accounts for 5 to 10% of all diabetes patients and is on the rise. The last decade has seen an average annual increase in the incidence of type 1 diabetes of 3%. T1DM affects 542 000 children under the age of 14, with boys somewhat more affected. About 78 000 new cases of type 1 diabetes are diagnosed globally every year. Today, type 1 diabetes affects 18.6 million individuals worldwide, and the number is expected to increase to almost 27.6 million by 2030. The incidence of T1DM was 15 per 100 000 people and the prevalence was 9.5% in the world (1, 2, 3).

In Serbia, in average 160 new cases of type 1 diabetes gets diagnosed each year, resulting in an incidence rate of 13.5 per 100 000 inhabitants. It is an estimate that in our country approximately 1400 children under the age of 15 have contracted this type of diabetes. Serbian children have a medium risk of developing type 1 diabetes when compared

to other European nations. T1DM has a risk of 0.4% in the general population. If the mother has T1DM, the child is at a 1% risk, whereas if the father is sick, the child is at a 3% risk. The risk of siblings getting sick is 6%, and the risk of getting sick in monozygotic twins is as high as 27% (4, 5).

Type 1 diabetes occurs in people with a genetic predisposition, but only 20-30% of people develop the disease. T1DM that goes undiagnosed or untreated can lead to life-altering health issues in a variety of organs. It can cause heart attacks, strokes, nerve damage, eyesight loss, renal failure and leg amputation (5). Diabetic complications cause early death, due to diabetes directly and higher-than-optimal blood glucose indirectly. Patients incur financial costs due to diabetes and its consequences. Diabetes and diabetes-related health effects account for 5–20% of healthcare spending in most countries. This condition is a big burden for healthcare systems, emphasizing the importance of finding low-cost adjuvant therapy for diabetes patients. Methods of prevention have not yet been defined (4, 5, 6).

Type 1 diabetes mellitus is an autoimmune disease characterized by degeneration of β cells of the endocrine pancreas, leading to insulin deficiency. Disease etiology is comprised of a combination of environmental and genetic factors, but the exact biochemical pathways that cause it remain unclear. As with many autoimmune diseases, it usually develops over several months or years, and a reduction in the number of β cells from 80 to 90% is required for symptoms of type 1 diabetes to occur when patients are asymptomatic. C-peptide secretion, could be found at onset, during the so-called remission phase. This endogenous insulin secretion could completely disappear soon after diagnosis or persist over a long period of time (7).

In blood analysis of 90% of patients founded presence of circulating autoantibodies to islet cell autoantigens which is characteristic of type 1A T1DM. A small percentage of affected patients (<10%) are classified as autoantibody-negative patients who have type 1B T1DM or "idiopathic T1DM", which may include individuals with lacking measurable common autoantibody (8). GWAS (genome-wide association studies) has revealed more than 50 genetic risk areas and more than 60% of the candidate genes detected were expressed in islets and β cells, suggesting that these genes play a significant role in the development of T1DM. Moreover, genetic studies have revealed many immunological and metabolic pathways now linked to T1DM pathogenesis (9).

The pathogenesis of type 1 diabetes includes a genetic predisposition to the disease and external factors that activate the mechanisms that lead to the progressive loss of pancreatic cells. Type 1 diabetes is one of the most frequent chronic autoimmune disease worldwide. T1DM often clusters in individuals and families, seen in the formation of autoimmune polyendocrinopathy. The major histocompatibility complex (MHC) gene on the short arm of chromosome 6 has the most-genetic effect. The most important genetic loci that confer risk for the disease are HLA loci, which provides about 50% of the genetic susceptibility. The HLA antigens DQ2 and DQ8, tightly linked with DR3 and DR4, are the major common genetic predispositions. The DR3/4 diplotype carries the highest chance of developing T1DM.

These haplotypes raise risk in a synergistic way, and recent research indicates that they have an enhanced ability to present T1DM autoantigens to T cells (10, 11).

Although the HLA region provides the majority of genetic risk for T1DM, approximately 60 non-HLA genetic loci contain variations linked with increased risk of T1DM. Functional single nucleotide polymorphisms in genes involved in immune regulation, such as the protein tyrosine phosphatase non-receptor type 22 (PTPN22), the cytotoxic T-lymphocyte-associated antigen (CTLA4), the interleukin-2 Receptor (IL2Ra), the Vitamin D receptor (VDR), and the tumor necrosis factor (TNF), have been found to confer susceptibility to T1DM (12, 13).

The non-receptor type 22 protein tyrosine phosphatase is one of the most powerful and newly discovered loci of genetic susceptibility for T1DM. Its likely relation to clinical heterogeneity of the disease makes it an interesting and possibly attractive prospective therapeutic option. The SNP in PTPN22 has one of the highest reported odds ratios and as such it has been verified in many studies. Both, T cell receptor (TCR) and B cell receptor (BCR) signaling is negatively regulated by PTPN22. TCR and BCR signaling, as well as other adaptive and innate immune cell functions are affected by the diabetes-associated SNP in PTPN22 (rs2476601) (14, 15).

PTPN22 has a main role in controlling of immune cells activation and immune responses. It is responsible for intracellular signaling pathways that affect the level of T cell activity and their effector functions and prevent spontaneous activation of auto-reactive cells and the development of autoimmunity (16). PTPN22 is expressed in hematopoietic cells, immune cells, including immature and mature T and B lymphocytes, monocytes, macrophages, neutrophils, natural killer (NK) cells, and dendritic cells (DCs). PTPN22 gene is located on chromosome 1p13.3-p13.1 and encodes the lymphoid-specific tyrosine phosphatase (LYP).

LYP is composed of 807 amino acids and it is an important negative regulator of signal transduction via the T cell receptor (TCR) and forms a complex with the negative regulatory kinase C-SRC kinase (CSK). Src family tyrosine kinases act as a molecular switch to regulate various cellular events, including cell growth, division, differentiation and programmed death. LYP binds on C-terminal Src kinase (CSK). The LYP-Csk complex gets anchored to the cytoplasmic side of the cell membrane and inactivates LCK, which positively regulates T cell receptor (TCR) signaling after antigen recognition (17). TCR regulates various cellular activities including cell growth, differentiation, division and apoptosis. Although only its role in T cell signaling regulation has been defined, it is probable that LYP regulates numerous pathways in immune cell activation and differentiation. Inhibitory functions of LYP are: negative effects on clonal expansion, T cell differentiation and TCR signaling (18). In addition to this, failure of thymic selection and peripheral control mechanisms against self-reactive T cells is essential for T1DM onset. LYP function in B lymphocytes are similar to that of T lymphocytes. The functions of Treg cells are also depended of LYP proteins

and their role in suppressing autoimmune reactions. Autoreactive lymphocytes may in turn derive from the emission of β cell autoantigens and inflammatory mediators by unknown pathogenic factors (19, 20).

Polymorphisms in PTPN22 are associated with several autoimmune diseases such as: T1DM, systemic lupus erythematosus and rheumatoid arthritis. Carriers of several PTPN22 polymorphisms have been shown to have a dysregulation in T cell activation leading to increased susceptibility to some autoimmune diseases. C1858 T is one of the most studied LYP variations, resulting from an SNP at position 1858 causing an arginine to a tryptophan substitution in exon 14 at position 620 (R620W). This mutation results in partial or complete disruption of PTPN22 CSK binding. The C1858T polymorphism within this gene contributes to the development of T1DM because it reduces the activation of T lymphocytes. It is believed that during the development of autoreactive T lymphocytes in the thymus, due to the reduction of their activity caused by the mentioned polymorphism, their survival occurs, and as such they can cause autoimmune reactions. The importance of T lymphocyte activation was highlighted by the discovery of the PTPN22 gene and its association with DM1 production (21, 22).

An increased incidence of the C1858 T variant has been found in several autoimmune diseases. Starting with Bottini et al. who were the first to discover C1858 T in 2004 and show its correlation with T1DM and who was shortly followed by many other Authors since then, all of which confirmed in various combined case-control and family-based association studies the link between the PTPN22 variant and T1DM among other autoimmune diseases. Xuan et al. described in the meta analysis that males who carried the C1858 T allele were more susceptible to T1DM than females (23) while Wang proposes this SNP as a considerable risk factor for T1DM among the Caucasian population (24). Therefore, all these studies imply that C1858 T may be associated with an increased risk of T1DM, particularly in European and American populations (25).

Many publications have looked at a possible link with disease variability: age at onset, autoantibodies, residual B cell function, and metabolic control quality, taking into consideration the well-established function of the C1858 T variation as a risk factor for T1DM. Some findings suggest a direct and indirect correlation between PTPN22 and earlier onset of the disease and β cell depletion after the initial auto-immune damage, respectively. Other results imply association with lower age at onset in female patients while most results show an increased frequency or levels of glutamic acid decarboxylase (GAD) autoantibodies and strong connection between GAD positivity and the PTPN22 C1858 T allele.

A lot of studies confirmed that T1DM onset is linked to autoreactive CD4+ and CD8+ T cell expansion, innate immune system activation, and autoantibody production. CD4+ cells release IL-2, IFN-γ, TNF-α, and TNF-β after the presentation of autoantigens by macrophages in pancreatic lymphocytes. In physiologic conditions, abnormal Th1 response is inhibited by Tregs. CD8+ T cells are activated and contribute to β cell destruction in conjunction with cytotoxic macrophages (26).

Moreover, B cells autoantibodies seem to play an indirect pathogenic role, and they also may be involved as antigen-presenting cells for CD4+ T lymphocytes, but their role is still under debate. B cell autoantibodies are a common characteristic of T1DM and the gold standard biomarker for islet autoimmunity and T1DM development. The SNP in PTPN22, rs2476601, is linked to a higher incidence of islet autoimmunity (i.e., autoantibodies directed against insulin, GAD65, or IA-2). The importance of B cells has been demonstrated in preclinical models and clinical trials. B cell depletion slows the loss of β cell function in newly diagnosed T1DM patients and can prevent illness in NOD mice (26, 27).

Conclusion

In recent years, immunologists have tried to exploit immunotherapeutic strategies for treating and/or preventing autoimmune diseases. The goal of these strategies should be to eliminate autoimmune processes before the complete loss of ability of cells, that is, pancreatic β cells in T1DM, in order to ensure adequate blood glucose levels.

The research of potential immunotherapeutic implications has mostly been focused on development of compounds able to selectively inhibit LYP while most of the unsolved questions seem to be related to the LYP inhibitors selectivity and clinical efficacy. However, this research area shows a lot of potential for development of T1DM secondary (prevention of clinical onset) and tertiary (preserving the remaining β cells in recently diagnosed subjects) preventive treatments and even the prospective chance for application in screening tests, whereas T1DM patients with PTPN22 variant represent a promising target group for prevention trials with highly selective LYP inhibitors (20).

References:

1. Mobasseri M, Shirmohammadi M, Amiri T, Vahed N, Hosseini Fard H, Ghojazadeh M. Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis. Health Promot Perspect. 2020; 10(2):98-115. doi: 10.34172/hpp.2020.18. PMID: 32296622; PMCID: PMC7146037.
2. Rak K, Bronkowska M. Immunomodulatory Effect of Vitamin D and Its Potential Role in the Prevention and Treatment of Type 1 Diabetes Mellitus-A Narrative Review. Molecules. 2018; 24(1):53. doi: 10.3390/molecules24010053. PMID: 30586887; PMCID: PMC6337255.
3. Díez-Fernández A, Ruiz-Grao MC, Mesas AE, Martinez-Vizcaino V, Garrido-Miguel M. Type 1 diabetes incidence trends in children and adolescents aged 0-14 years in Europe: a systematic review and meta-analysis protocol. BMJ Open. 2021; 11(10):e054962. doi: 10.1136/bmjopen-2021-054962. PMID: 34667016; PMCID: PMC8527137.
4. Vojislav C, Natasa R, Milica P, Slobodan A, Radivoj K, Danijela R, Sasa R. Incidence trend of type 1 diabetes mellitus in Serbia. BMC Endocr Disord. 2020; 20(1):34. doi: 10.1186/s12902-020-0504-y. PMID: 32151244; PMCID: PMC7063701.

5. World Health Organization Global Report on Diabetes. [(accessed on 17 September 2018)];2016 Available online: http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf;jsessionid=CCC2429A03D7EF6D638C05F6F008A3C2?sequence=1.
6. Al-Lawati JA. Diabetes Mellitus: A Local and Global Public Health Emergency! Oman Med J. 2017; 32(3):177-179. doi: 10.5001/omj.2017.34. PMID: 28584596; PMCID: PMC5447787.
7. Robertson CC, Rich SS. Genetics of type 1 diabetes. Curr Opin Genet Dev. 2018; 50:7-16. doi: 10.1016/j.gde.2018.01.006. Epub 2018 Feb 14. PMID: 29453110.
8. Redondo MJ, Steck AK, Pugliese A. Genetics of type 1 diabetes. Pediatr Diabetes. 2018; 19(3):346-353. doi: 10.1111/pedi.12597. Epub 2017 Nov 2. PMID: 29094512; PMCID: PMC5918237.
9. Oram RA, Redondo MJ. New insights on the genetics of type 1 diabetes. Curr Opin Endocrinol Diabetes Obes. 2019; 26(4):181-187. doi: 10.1097/MED.0000000000000489. PMID: 31219823.
10. Paschou SA, Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C. On type 1 diabetes mellitus pathogenesis. Endocr Connect. 2018; 7(1):R38-R46. doi: 10.1530/EC-17-0347. Epub 2017 Nov 30. PMID: 29191919; PMCID: PMC5776665.
11. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018; 391(10138):2449-2462. doi: 10.1016/S0140-6736(18)31320-5. PMID: 29916386; PMCID: PMC6661119.
12. Jovic M, Cvetkovic V, Despotovic M, Jevtovic Stoimenov T. The association of genetic polymorphisms with diabetes mellitus type 1. Acta Medica Medianae. 2020; 59(1): 125-132. doi:10.5633/amm.2020.0118.
13. Frommer L, Kahaly GJ. Type 1 Diabetes and Autoimmune Thyroid Disease-The Genetic Link. Front Endocrinol (Lausanne). 2021; 12:618213. doi: 10.3389/fendo.2021.618213. PMID: 33776915; PMCID: PMC7988207.
14. Armitage LH, Wallet MA, Mathews CE. Influence of PTPN22 Allotypes on Innate and Adaptive Immune Function in Health and Disease. Front Immunol. 2021; 12:636618. doi: 10.3389/fimmu.2021.636618. PMID: 33717184; PMCID: PMC7946861.
15. Burn GL, Cornish GH, Potrzebowska K, Samuelsson M, Griffié J, Minoughan S, Yates M, Ashdown G, Pernodet N, Morrison VL, Sanchez-Blanco C, Purvis H, Clarke F, Brownlie RJ, Vyse TJ, Zamoyska R, Owen DM, Svensson LM, Cope AP. Superresolution imaging of the cytoplasmic phosphatase PTPN22 links integrin-mediated T cell adhesion with autoimmunity. Sci Signal. 2016; 9(448):ra99. doi: 10.1126/scisignal.aaf2195. PMID: 27703032.
16. Bottini N, Vang T, Cucca F, Mustelin T. Role of PTPN22 in type 1 diabetes and other autoimmune diseases. Semin Immunol. 2006; 18(4):207-13. doi: 10.1016/j.smim.2006.03.008. Epub 2006 May 11. PMID: 16697661.
17. Clark M, Kroger CJ, Ke Q, Tisch RM. The Role of T Cell Receptor Signaling in the Development of Type 1 Diabetes. Front Immunol. 2021; 11:615371. doi: 10.3389/fimmu.2020.615371. PMID: 33603744; PMCID: PMC7884625.
18. Concannon P, Rich SS, Nepom GT. Genetics of type 1A diabetes. N Engl J Med. 2009;360(16):1646-54. doi: 10.1056/NEJMra0808284. PMID: 19369670.
19. Rodríguez A, Alfaro JM, Balthazar V, Pineda Trujillo N. Association analysis of PTPN22, CTLA4 and IFIH1 genes with type 1 diabetes in Colombian families. J Diabetes. 2015; 7(3):402-10. doi: 10.1111/1753-0407.12192. Epub 2014 Sep 10. PMID: 25042601.
20. Prezioso G, Comegna L, Di Giulio C, Franchini S, Chiarelli F, Blasetti A. C1858T Polymorphism of Protein Tyrosine Phosphatase Non-receptor Type 22 (PTPN22): an eligible target for prevention of type 1 diabetes? Expert Rev Clin Immunol. 2017; 13(3):189-196. doi: 10.1080/1744666X.2017.1266257. Epub 2016 Dec 8. PMID: 27892782.
21. Blasetti A, Di Giulio C, Tumini S, Provenzano M, Rapino D, Comegna L, Prezioso G, Chiuri R, Franchini S, Chiarelli F, Stuppia L. Role of the C1858T polymorphism of protein tyrosine phosphatase non-receptor type 22 (PTPN22) in children and adolescents with type 1 diabetes. Pharmacogenomics J. 2017; 17(2):186-191. doi: 10.1038/tpj.2016.6. Epub 2016 Feb 23. PMID: 26902538.
22. Alswat KA, Nasr A, Al Dubayee MS, Talaat IM, Alsulaimani AA, Mohamed IAA, Allam G. The Potential Role of PTPN-22 C1858T Gene Polymorphism in the Pathogenesis of Type 1 Diabetes in Saudi Population. Immunol Invest. 2018;47(5):521-533. doi: 10.1080/08820139.2018.1458109. Epub 2018 Apr 3. PMID: 29611765.
23. Xuan C, Lun LM, Zhao JX, Wang HW, Zhu BZ, Yu S, Liu Z, He GW. PTPN22 gene polymorphism (C1858T) is associated with susceptibility to type 1 diabetes: a meta-analysis of 19,495 cases and 25,341 controls. Ann Hum Genet. 2013; 77(3):191-203. doi: 10.1111/ahg.12016. Epub 2013 Feb 26. PMID: 23438410.
24. Wang S, Dong H, Han J, Ho WT, Fu X, Zhao ZJ. Identification of a variant form of tyrosine phosphatase LYP. BMC Mol Biol. 2010; 11:78. doi: 10.1186/1471-2199-11-78. PMID: 21044313; PMCID: PMC2987843.
25. Lee YH, Song GG. Meta-analysis of the family-based association between the PTPN22 C1858T polymorphism and type 1 diabetes. Mol Biol Rep. 2013; 40(1):211-5. doi: 10.1007/s11033-012-2051-8. Epub 2012 Oct 8. PMID: 23054006.
26. Valta M, Gazali AM, Viisanen T, Ihantola EL, Ekman I, Toppari J, Knip M, Veijola R, Ilonen J, Lempainen J, Kinnunen T. Type 1 diabetes linked PTPN22 gene polymorphism is associated with the frequency of circulating regulatory T cells. Eur J Immunol. 2020; 50(4):581-588. doi: 10.1002/eji.201948378. Epub 2019 Dec 19. PMID: 31808541.
27. Marca V, Gianchecchi E, Fierabracci A. Type 1 Diabetes and Its Multi-Factorial Pathogenesis: The Putative Role of NK Cells. Int J Mol Sci. 2018; 19(3):794. doi: 10.3390/ijms19030794. PMID: 29534427; PMCID: PMC5877655.

Primljen/Received: 8.3.2022.
Prihvaćen/Accepted: 16.3.2022.

Correspondance to:
Dr med. Maja Jović
18000 Niš, Patrisa Lumumbe 45/53.
Mail: drmajaj@