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Oral tolerance therapy in type 1 diabetes mellitus

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Type 1 diabetes mellitus (T1DM), an autoimmune disorder, is marked by T cell-mediated destruction of the β cells of the pancreas, which leads to an almost complete loss of the ability to synthesize insulin.[1] This insulin deficiency results in loss of the ability to regulate blood sugar, therefore, exogenous insulin administration is necessary for patients to control blood sugar and to reduce the incidence of related chronic diabetic complications.[2] In addition, a positive correlation between diabetes mellitus and hypertension has been detected.[3]

During the development of T1DM, the autoimmune attack of β cells of the pancreas mediated by T cells is regarded as the final step.[4] Typical T1DM-related autoantibodies target various proteins.[1,5] Various autoantibodies can be observed many months or years before clinical onset. These autoantibodies can be considered biomarkers of β-cell injury rather than its cause. The mechanism triggering this autoimmune process remains elusive, and this is the most crucial challenge preventing T1DM. Studies to date propose that interactions between genetic susceptibility and environmental exposures are necessary in the development of T1DM. Compared to the relatively well-known genetic factors,[6] environmental determinants remain poorly understood despite intensive research. Studies have shown that diet, virus infection, and the bacterial microbiome in the gastrointestinal tract (GIT) are associated with T1DM.[1,7,8] Currently, few studies on successfully preventing the onset of T1DM have been reported.[9]

Oral tolerance represents an adaptation, an unresponsiveness or a hyporesponsiveness to an orally administered antigen by the immune system. Thus, this process functions importantly in maintaining a balance between reactions against these exogenous antigens and body self-components.[10] As a physiological response to dietary antigens, oral tolerance mainly develops in the GIT. Although most of the orally delivered antigens are digested into short peptides and/or amino acids, a small amount of intact antigens can reach the intestinal epithelium.[11] Composed of Peyer patches (PPs) and mesenteric lymph nodes (MLNs), gut-associated lymphoid tissue (GALT) functions heavily in inducing oral tolerance. Based on various proposed routes for antigens passing through the intestinal epithelium,[11] $CD103^+$ dendritic cells (DCs) harboring autoantigens derived from the gut move to the MLNs,[12] which have been identified as an important site of oral tolerance induction.[13] However, compared to the MLN, PPs may not be necessary for oral tolerance induction.[14] In the MLN, $CD103^+$ DCs harboring antigens meet naïve $CD4^+$ and $CD8^+$ T cells, and oral tolerance induction occurs in an antigen dose-dependent manner, including low- and high-dose tolerance.[11,15] With repeated encounters with low-dose antigens, the resultant regulatory T cells (Tregs) help to induce oral tolerance. With a single encounter with high-dose antigen, anergy and/or deletion of antigen-specific T cells is induced in GALT, which contributes to oral tolerance.[10]

As T1DM is a predictable disease, individuals at risk for it may be identified years before clinical onset.[7] This makes oral tolerance, which acts as an antigen-specific immunotherapy (ASI), an attractive treatment for delaying and/or preventing T1DM.[16] Based on the formula used, oral tolerance trials performed in non-obese diabetic (NOD) mice can be divided into two types, including direct oral administration of a single autoantigen and combinatorial therapy. The latter may be further divided into the following types, including a combination of different

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autoantigens and a combination of autoantigen(s) with various delivery vehicles and/or immune adjuvants and/or immunomodulatory agents. Recently, T1DM was prevented in all immunized NOD mice by oral administration of HSP65-6×P277-loaded gut DCs-targeting nanoparticles, and oral tolerance induction was achieved by repairing Th1/Th2 imbalance and increasing the functional $CD4^+Foxp3^+CD25^+$ Tregs proportions.[17] Oral administration of a single-chain insulin analog, which was delivered by bacterium-like particles, could suppress the process of T1DM in NOD mice through a similar mechanism.[18]

Compared to oral tolerance trials in animals, in human clinical trials, insulin is the only used T1DM autoantigen. Oral insulin (7.5 mg/day) had no effect on delaying or preventing T1DM in people who were autoantibody positive; however, a beneficial effect of delaying T1DM onset in patients with confirmed insulin autoantibody (IAA) levels ≥80 nU/mL was observed by sub-group analyses.[19,20] These results suggested that IAA levels may be a key recruitment criterion for such studies. As a primary prevention trial, the Pre-POINT randomized clinical trial showed that oral insulin (67.5 mg/day) led to a regulatory immune response without hypoglycemia in T1DM-high-risk children who bore no signs of islet autoimmunity. The enhanced saliva IgG towards insulin and regulatory profiles of T cells responding to insulin among treated individuals indicated the successful induction of oral tolerance.[21]

Working as an ASI, oral tolerance therapy, if applied properly, exhibits the ability to restore the immune system towards durable tolerance to disease-related autoantigen (s). Most previous study indicate that oral administration of T1DM-related autoantigens exhibits a positive effect to prevent, delay or reverse the disease in NOD mice. However, these preclinical reports are somewhat conflicting with respect to the timing of therapy initiation, frequency and dosage of autoantigen administration, treatment duration, type of autoantigen applied, demand for combinational reagents and, perhaps most importantly, degree of efficacy. In addition, there are some reports indicating that oral autoantigen therapy exhibits no effect on delaying or preventing the onset of T1DM in animal models, possibly because antigens passing through the GIT are degraded, which leads to little autoantigen reaching the mucosal immune surface and subsequently influences tolerance induction.

Although some oral insulin therapies for T1DM have been shown to be effective in animals, their clinical translation has not been achieved. Some important differences related to the progression of T1DM in animal models and humans may be responsible for this translation failure. Furthermore, compared to mouse models, humans exhibit more complicated regulation of the immune system, which may result in lower immune response to similar dosages of autoantigens. In addition, it should be noted that efficacy rather than safety is more addressed during the design and implementation of animal studies, and the potential treatment-associated complications are less investigated or documented. However, the safety of oral tolerance induction should be considered when designing clinical trials, therefore, among the performed clinical trials, a lower dose of orally administered autoantigens is applied, and some combinational therapies using various delivery vehicles, immune adjuvants or immunomodulatory agents have not been introduced.

As an antigen-based immunotherapy, we believe that oral tolerance therapy shows promise for restoring immune tolerance to autoantigen(s) and subsequently preventing, delaying or reversing T1DM. To achieve this aim in human clinical trials, the following factors need to be carefully considered. First, immune biomarkers with improved sensitivity and specificity are needed to identify individuals at risk of T1DM as early as possible. Second, since T1DM is a heterogeneous disease,[22] all patients might not exhibit a similar response to one therapy strategy. Therefore, more personalized strategies for tolerance induction may be needed. Third, the results obtained from animal and human tests have shown that it may be far easier to prevent T1DM by oral tolerance therapy than to arrest or reverse its effects after clinical onset. Therefore, assuming it is safe, oral tolerance therapy should be introduced in at-risk subjects, who are often children, as early as possible before clinical onset. Finally, animal studies have indicated that combinational therapies consisting of autoantigen administration with immune adjuvants and/or immunomodulatory agents possess the potential to safely prevent or stably reverse disease processes. Such combination studies in humans, which may be difficult to conduct, have not been published; however, these strategies still exhibit high therapeutic potential.

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Conflicts of interest

None.

References

1. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet 2018;391:2449–2462. doi: 10.1016/S0140-6736(18)31320-5.
2. Meetoo D, McGovern P, Safadi R. An epidemiological overview of diabetes across the world. Br J Nurs 2007;16:1002–1007. doi: 10.12968/bjon.2007.16.16.27079.
3. Zeng XT, Weng H, Jin YH, Liu TZ, Liu MY, Wang XH. Association between diabetes mellitus and hypertension in benign prostatic hyperplasia patients. Chin Med J 2018;131:1120–1121. doi: 10.4103/0366-6999.230730.
4. Roep BO. The role of T-cells in the pathogenesis of Type 1 diabetes: from cause to cure. Diabetologia 2003;46:305–321. doi: 10.1007/s00125-003-1089-5.
5. Yi B, Huang G, Zhou ZG. Current and future clinical applications of zinc transporter-8 in type 1 diabetes mellitus. Chin Med J 2015;128:2387–2394. doi: 10.4103/0366-6999.163389.
6. 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.

7. Regnell SE, Lernmark A. Early prediction of autoimmune (type 1) diabetes. Diabetologia 2017;60:1370–1381. doi: 10.1007/s00125-017-4308-1.
8. Qi CJ, Zhang Q, Yu M, Xu JP, Zheng J, Wang T, *et al*. Imbalance of fecal microbiota at newly diagnosed type 1 diabetes in Chinese children. Chin Med J 2016;129:1298–1304. doi: 10.4103/0366-6999.182841.
9. Dayan CM, Korah M, Tatovic D, Bundy BN, Herold KC. Changing the landscape for type 1 diabetes: the first step to prevention. Lancet 2019;394:1286–1296. doi: 10.1016/S0140-6736(19)32127-0.
10. Rezende RM, Weiner HL. History and mechanisms of oral tolerance. Semin Immunol 2017;30:3–11. doi: 10.1016/j.smim.2017.07.004.
11. Tordesillas L, Berin MC. Mechanisms of oral tolerance. Clin Rev Allergy Immunol 2018;55:107–117. doi: 10.1007/s12016-018-8680-5.
12. Schulz O, Jaensson E, Persson EK, Liu X, Worbs T, Agace WW, *et al*. Intestinal CD103+, but not CX3CR1+, antigen sampling cells migrate in lymph and serve classical dendritic cell functions. J Exp Med 2009;206:3101–3114. doi: 10.1084/jem.20091925.
13. Worbs T, Bode U, Yan S, Hoffmann MW, Hintzen G, Bernhardt G, *et al*. Oral tolerance originates in the intestinal immune system and relies on antigen carriage by dendritic cells. J Exp Med 2006; 203:519–527. doi: 10.1084/jem.20052016.
14. Kraus TA, Brimnes J, Muong C, Liu JH, Moran TM, Tappenden KA, *et al*. Induction of mucosal tolerance in Peyer's patch-deficient, ligated small bowel loops. J Clin Invest 2005;115:2234–2243. doi: 10.1172/JCI19102.
15. Sricharunrat T, Pumirat P, Leaungwutiwong P. Oral tolerance: recent advances on mechanisms and potential applications. Asian Pac J Allergy Immunol 2018;36:207–216. doi: 10.12932/AP0848.
16. Harrison LC, Wentworth JM, Zhang Y, Bandala-Sanchez E, Bohmer RM, Neale AM, *et al*. Antigen-based vaccination and prevention of type 1 diabetes. Curr Diab Rep 2013;13:616–623. doi: 10.1007/s11892-013-0415-7.
17. Chen Y, Wu J, Wang J, Zhang W, Xu B, Xu X, *et al*. Targeted delivery of antigen to intestinal dendritic cells induces oral tolerance and prevents autoimmune diabetes in NOD mice. Diabetologia 2018;61:1384–1396. doi: 10.1007/s00125-018-4593-3.
18. Mao R, Chen Y, Wu Q, Zhang T, Diao E, Wu D, *et al*. Oral delivery of single-chain insulin (SCI-59) analog by bacterium-like particles (BLPs) induces oral tolerance and prevents autoimmune diabetes in NOD mice. Immunol Lett 2019;214:37–44. doi: 10.1016/j.imlet.2019.08.008.
19. Skyler JS, Krischer JP, Wolfsdorf J, Cowie C, Palmer JP, Greenbaum C, *et al*. Effects of oral insulin in relatives of patients with type 1 diabetes: the diabetes prevention trial–type 1. Diabetes Care 2005;28:1068–1076. doi: 10.2337/diacare.28.5.1068.
20. Vehik K, Cuthbertson D, Ruhlig H, Schatz DA, Peakman M, Krischer JP, *et al*. Long-term outcome of individuals treated with oral insulin: diabetes prevention trial-type 1 (DPT-1) oral insulin trial. Diabetes Care 2011;34:1585–1590. doi: 10.2337/dc11-0523.
21. Bonifacio E, Ziegler AG, Klingensmith G, Schober E, Bingley PJ, Rottenkolber M, *et al*. Effects of high-dose oral insulin on immune responses in children at high risk for type 1 diabetes: the Pre-POINT randomized clinical trial. JAMA 2015;313:1541–1549. doi: 10.1001/jama.2015.2928.
22. Ilonen J, Lempainen J, Veijola R. The heterogeneous pathogenesis of type 1 diabetes mellitus. Nat Rev Endocrinol 2019;15:635–650. doi: 10.1038/s41574-019-0254-y.

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