Zinc Transporter 8 (ZnT8) and its role in the diagnosis of Type 1 Diabetes Mellitus

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Abstract

Diabetes is one of the most challenging chronic and heterogeneous diseases all over the world. For now it is already established, that in most of the cases Diabetes Type 1 results from autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans. The combined measurement of zinc transporter 8 antibodies (ZnT8A), glutamic acid decarboxylase antibodies (GADA), insulinoma associated autoantigen 2 antibodies (IA2A), and insulin antibodies (IAA) raised autoimmunity detection rates to 98% at disease onset. Zinc (Zn) plays essential roles in cellular metabolism of mammals. The pancreatic islet β-cell is among the cells which contain high levels of zinc. It is concentrated in the insulin secretory granules and is essential for the proper storage, secretion, and the action of insulin. Zinc transport in mammals is regulated by the family of Zn transporters. ZnT8 is expressed in pancreatic islet β-cells. The essential role of this protein is to transports zinc ions from the cytosol into the vesicles of β-cells for insulin secretion and storage. ZnT8 is one of main antigens in the etiology of type 1 diabetes mellitus and it can be used as diagnostic and predictive tool for Type 1 Diabetes Mellitus. Though the onset of type 1 diabetes cannot be prevented, it is still very important to reveal the different risk groups as the knowledge of the increased risk can help to prevent acute onset of the disease with ketoacidosis and concomitant morbidities. (TCM-GMJ October 2016; 1(2):P26-P28)

Keywords: Diabetes, Autoimmunity, ZnT8, Antibodies

Introduction

Diabetes is one of the most challenging chronic and heterogeneous diseases all over the world1. It interrupts normal development in children and carries the threat of severe complications in the most active period of life. For now it is already established, that in most of the cases Diabetes Type 1 results from autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans3. Though type 1 diabetes mellitus is less common, than type 2 diabetes, it is the major autoimmune diabetes in humans1. The treatment strategies for patients with diabetes mellitus vary widely and are depending on the accurate determination of the type of diabetes. The combined measurement of zinc transporter 8 antibodies (ZnT8A), glutamic acid decarboxylase antibodies (GADA), insulinoma associated autoantigen 2 antibodies (IA2A), and insulin antibodies (IAA) raised autoimmunity detection rates to 98% at disease onset. ZnT8A were persistent in the prediabetic phase and proved to be a useful independent marker of autoimmunity either alone in antibody-negative subjects or in conjunction with IAA, GADA, or IA2A3. Though the onset of type 1 diabetes cannot be prevented, it is still very important to reveal the different risk groups as the knowledge of the increased risk can help to prevent acute onset of the disease with ketoacidosis and concomitant morbidities.

The role of zinc in the biosynthesis of insulin

Zinc plays essential role in cellular metabolism of mammals. The pancreatic islet β-cell is among the cells which contain high levels of zinc4. There is large evidence that zinc status and homeostasis plays the essential role in the onset and progression of diabetes5,6. Zinc supplementation to the meal had inhibited the progression of the experimental type 1 diabetes in rodents7. Zn is concentrated in the insulin secretory granules of pancreatic islet β-cells and is essential for the proper storage, secretion, and the action of insulin. Proinsulin which is formed from preproinsulin after cleavage of the signal sequence, is assembled in the Golgi apparatus in hexameric form forming zinc-calcium-proinsulin complex, the histidine at amino acid position 10 in the B-chain (His B10) coordinates the two central zinc ions. Then by excision of the C-peptide with proteolytic enzymes the hexameric proinsulin is converted into the insulin hexamer. Therefore Zn is essential for structural stability of stored insulin. Zinc transport in mammals is regulated by the family of Zn transporters. Zn is co-released with insulin into extracellular fluid over the exocytosis of insulin from β-cell and releases from insulin when it reaches the blood, which

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has higher pH, then extracellular fluid. There is a consideration, that these released Zn ions play a role in regulation of a pancreatic α cell secretory function.

Zinc Transporters

The homeostasis of zinc is regulated by ZnT (SLC30A) and Zip (SLC39A) transporters. ZnT transporters transport zinc ions from cytoplasm into extracellular fluid or lumen of organelles, thus decreasing intracellular zinc level. On the contrary Zip transporters transport zinc ions from extracellular space to the cytoplasm and increases the level of intracellular zinc ions. Currently there were identified 10 members of the ZnT family (ZnT1 to ZnT10) and 14 members of the Zip family (Zip1 to Zip14).

In pancreatic islet β-cells Zn ions from cytoplasm to insulin secreting vesicles is transported by the enzyme ZnT8 (SLC30A). It is localized to insulin containing secretory granules and its main function is to provide Zn to β-cells for insulin secretion and storage.

ZnT8 antibodies – diagnostic tool for diabetes mellitus

ZnT8 has recently been identified as one of the major antigens in pathogenesis of type 1 diabetes mellitus. The antibodies to this antigen were discovered by the works of Wenzlau et al. They studied mRNA of human and rodent pancreatic cells. 223 patients with new onset type 1 diabetes mellitus were included in the study. GAD, IA-2 and IA antibodies were detected respectively in 72%, 68%, 55%, and 63% of new-onset patients (n 223). ZnT8A measurements, if substituted individually for GADA, IA2A, or IAA, detected a similar number of diabetic patients; inclusion of the ZnT8 assays in the list of assays for detection of autoimmunity to pancreatic β-cells reduced the number of diabetic autoantibody-negative individuals from 5.8% to 1.8% and increased the number who tested positive for two or more autoantibodies from 72% to 82%.

In 2010 has been published another study showing, that ZnT8 antibodies seems to be a valuable marker to differentiate clinical phenotypes of diabetes mellitus. ZnT8 antibodies has been tested in 193 patients with latent autoimmune diabetes of adults (LADA), who were positive for GAD and IA-2 antibodies and in 1056 antibody negative patients with type 2 diabetes mellitus. ZnT8 antibodies were detected in 18.6% patients with autoimmune diabetes and 1.4% with type 2 diabetes. This study demonstrated, that the use of GAD, IA-2 and ZnT8 antibodies in combination allowed a stratification of clinical phenotype, with younger age of onset of diabetes and more severe insulin deficiency in patients with all three markers.

The role of ZnT8 antibodies and ZnT8 encoding gen SLC30A8 (Solute carrier family 30 (zinc transporter), member 8) in the pathogenesis of type 1 diabetes mellitus has been also revealed by the study conducted in Germany – BABYDIAB. It was multicentral, prospective, cohort study. ZnT8 autoantibodies were measured in sera of 1,633 children with a first-degree family history of type 1 diabetes mellitus and who were prospectively followed from birth. To reveal single nucleotide polymorphism SLC30A8 genotyping has been performed in 1,170 children. ZnT8 autoantibodies were detected in 58 children as early as 9 months of age (median 3 years). Among 128 children who were positive for GAD, IA-2 or insulin antibodies, ZnT8 antibodies were detected in 55 (43%) and 34 (81%) children from those 42 who developed diabetes, were positive for ZnT8 antibodies. The additional presence of ZnT8 antibodies stratified diabetes risk in islet autoantibody-positive children. The same study showed, that SLC30A8 genotype strongly influenced ZnT8 antibody type and diabetes risk in ZnT8A positive children.

The role of ZnT8 antibodies in prediction of type 1 diabetes mellitus

Several studies had revealed, that positivity to autoantibodies to pancreatic islet cells, especially multiple antibody positivity can be used for screening of people with high risk of type 1 diabetes mellitus. Among the individuals with first degree relatives with type one diabetes mellitus, 6.1% is positive for GAD, IA-2 and/or ZnT8 antibodies, within the follow-up period 34% of antibody positive subjects developed type 1 diabetes mellitus. In first degree relatives of patients with type 1 diabetes mellitus, who were positive for GAD or IA-2 the risk of developing type one diabetes in the observational period of 4 – and 5 years were 7% and 17% respectively. When ZnT8 antibodies measurement was added the cumulative risk has increased up to 31% and 47% respectively.

Adding ZnT8 antibodies to IA-2 antibodies appeared more cost-effective strategy to identify individuals with high risk of progression to type 1 diabetes mellitus. It allowed to identify 78% of first degree relatives who developed diabetes within 5 year, especially under the age of 40 years.

Conclusion

Type 1 Diabetes mellitus, is an organ – specific autoimmune disease which is caused by a complex interaction of genetic and environmental factors. It interrupts normal development in children and carries the threat of severe complications in the most active period of life. Most patients with newly diagnosed type 1 diabetes mellitus have elevated concentrations of auto-antibodies against Langherans islet β cells. The antigens for these antibodies are insulin, glutamic acid decarboxylase (GAD), insulinoma associated autoantigen 2 (IA2), and zinc transporter 8 (ZnT8). ZnT8 has recently been identified as one of the major antigens in pathogenesis of type 1 diabetes mellitus. Zinc plays essential roles in cellular metabolism of mammals. The pancreatic islet β-cell is among the cells which contain high levels of zinc. There is large evidence that zinc status and homeostasis plays the essential role in the onset and progression of diabetes. The homeostasis of zinc is regulated by ZnT (SLC30A) and Zip (SLC39A) transporters. In pancreatic islet β-cells Zn ions from cytoplasm to insulin secreting vesicles is transported.
by the enzyme ZnT8 (SLC30A). It is localized to insulin containing secretory granules and its main function is to provide Zn to β-cells for insulin secretion and storage. ZnT8 is one of main antigens in the etiology of type 1 diabetes mellitus and it can be used as diagnostic and predictive tool for Type 1 Diabetes Mellitus. Though the onset of type 1 diabetes cannot be prevented, it is still very important to reveal the different risk groups as the knowledge of the increased risk can help to prevent acute onset of the disease with ketoacidosis and concomitant morbidities.

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