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The Importance of the Variability of Leucocyte Zinc Transporter 8 (ZnT8) Gene Expression

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The variability of ZnT8 expression in leukocytes develops in patients with a genetic predisposition to this condition and it decreases with age. Greater intercellular zinc accumulation may potentially provoke increased levels of its expression, as a support mechanism in zinc homeostasis. The occurrence of ZnT8 antibodies (ZnT8A) may result in leukocyte dysfunction, which is dependent i.a. on the level of ZnT8 expression. The same correlation can be observed in non-pancreatic tissues. ZnT8A occur in approximately 16.5% of research participants without any diabetes symptoms and the frequency of their occurrence decreases with age as well. The occurence of variability of ZnT8 expression in leukocytes and other tissues, and the occurrence of ZnT8A may be connected with development of autoimmune processes, not only such as diabetes mellitus t. 1.

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1. INTRODUCTION

Solute carrier (SLC) transporters – such as zinc transporters (ZnT) – play a key role in basic life processes, which include those taking place in the cells of the immune system [1-4].

Zinc transporter 8 (ZnT8) gene expression (SLC30A8) can be observed in in various cells, and its occurrence is not limited to pancreatic islet cells. Its level is dependent not only on regulating factors, but also on the structure of the gene itself.

Under physiological conditions, zinc transporter 8 (ZnT8) expression is characterised by high variability in leukocytes and was not observed in all the analysed samples, which is not the case of the majority of the remaining zinc transporters (ZnT) [5].

It was observed for the first time by Overbeck, Uciechowski, Ackland, Ford and Rink in 2008 [5]. Since then, subsequent observations of this phenomenon have been merely "a side effect" of other observations. Because the occurence of variability of ZnT8 expression in leukocytes and other tissues, and the occurrence of ZnT8A may be connected with development of autoimmune processes, not only such as diabetes mellitus t. 1 – it was the reason why we decided to review the literature.

The aim of this review the literature was to find the possible pathophysiological relationships of these phenomena.

2. METHODS

The internet data bases were searched including: Google, Google Scholar, Yahoo, and PUBMED. The search words that were used included, above all: leucocytes ZnT8 gene expression, ZnT8 gene expression, ZnT8 antibodies, ZnT8A. 25 references were identified which were used to write the review articles which had been divided into subsections including empirical review and preliminary hypothesis.

3. RESULTS

3.1 Empirical Review

Research conducted by Foster et al revealed that, at the mRNA level, zinc transporter 8 (ZnT8) expression could only be observed in 10 out of 40 healthy participants (6 women and 4 men), who constituted 17.5% of the research group. The latter included 7 participants under the age of 30 years that amounted to 70% of the participants. In this particular group, interindividual variability of zinc transporter 8 expression at the mRNA level was extremely high. Another study, conducted 3 months later, lead to the same conclusion [6].

Wex et al analysed 5 leukocyte samples from healthy research participants and observed zinc transporter 8 (ZnT8) expression in all of them, following phytohemagglutinin stimulation [7].

The expression of zinc transporter 8 (ZnT8) was identified by Chu et al, in the leukocytes from 16 (out of 38) study participants with type 2 diabetes (42%) [8].

In another study – involving post-menopausal women with type 2 diabetes mellitus (DMt2) higher HbA1c levels were measured in patients with the expression of zinc transporter 8 in leukocytes as compared to those participants in whom the expression in question did not occur. [9] In this particular research, the expression of zinc transporter 8 was observed in 21, out of 48, patients (43.75%).

With regard to high variability levels of the expression of zinc transporter 8 in leukocytes, this parameter is not taken into account as biomarker of zinc status in the human organism [10].

It was demonstrated that ZnT8 Arg325Trp single-nucleotide polymorphism (rs13266634) influenced zinc transporter 8 expression and cytokine production in leukocytes in patients with type 1 diabetes (DMt1). In the case of Arg/Arg polymorphism, higher intercellular free zinc concentration levels, higher levels of ZnT8 expression and increased cytokine production levels were observed [11].

The expression of zinc transporter 8 (ZnT8) was also identified in other non-pancreatic tissues, in organs, such as thyroid, adrenal glands [12], testicles [13], retina [14], kidneys [15] and heart [16].

It was revealed that erythropoietin inhibits the development of diabetic retinopathy in rats. It was observed that the retina of diabetic

rats and the hypoxia of retinal Müller cell line (rMC1) exhibit reduced levels of ZnT8 expression at the mRNA level and of the protein itself, with the accompanying increase in intercellular zinc content. Administration of erythropoietin prevented the increase in intercellular zinc content, which may have been due to increased levels of ZnT8 expression, resulting from the inhibited HIF-1a expression and the ERK pathway activation [14].

It was proved that the increase in ZnT8 expression levels in kidneys, in turn, inhibits the progression of renal interstitial fibrosis, constituting an element of diabetic nephropathy, through pathway inhibition – transforming growth factor β1 (TGF-β1)/ the Smad pathway activation [15].

It was demonstrated experimentally that the inhibition of ZnT8 gene expression in non-obese diabetes (NOD) mice impairs the autoimmune inflammatory response of the pancreas and its lesion [17]. The impairment of CD8+ T lymphocytes activation, accompanied by decreased levels of their cytotoxicity, was observed as a result of inhibited ZnT8 expression [17].

In vitro experiments demonstrated that decreased levels of ZnT8 activity prevented the inflammation of insulinoma cells in humans [18]. Similarly, it was demonstrated that ZnT8 deficits limited the extent of damage to hepatocytes resulting from exposure to acetaminophen, through the reduction of oxidative stress [19].

It can therefore be indirectly assumed that the absence of or low levels of ZnT8 expression in leukocytes protect them against inflammation and oxidative stress, and high levels of transporter 8 in leukocytes lead to increased risk of their dysfunction in the case of ZnT8A occurrence.

Researchers have been investigating the importance of ZnT8 as well as its genetic variability in the pancreas and non-pancreatic tissues for several years. Consequently, attempts have been made to systematise the relevant data for a long time.

In their review of the regulatory role played by zinc transporters in pancreatic islet cells, Bosco et al (2010) provided data confirming that ZnT8 shows varied immunogenicity levels, resulting from its genetic polymorphism, DMt1 progresses more rapidly in SLC30A8 SNP rs13266634 homozygotes as compared to heterozygotes, cyclosporine A shows varied levels of cytotoxicity in pancreatic islet cells and the transplantation of kidneys with ZnT8 gene polymorphism (SLC30A8) favours the development of post-transplant diabetes (PTDM) [20].

In a more recent review, entitled 'Potentially positive and negative consequences of ZnT8 inhibition', Syring et al proved that the lack of SLC30A8 gene in ZnT8, its haploinsufficiency, SNP (such as rs13266634) not only contribute to diabetes-related organ pathologies, glucose metabolism dependent on the developmental age, but also to haemolytic anaemia, morphological changes in erythrocytes, as well as the number of reticulocytes, platelets and lymphocytes [21]. The aforementioned data are the indicators of the non-pancreatic role of ZnT8 and, in the case of leukocytes, of its importance at the stage of differentiation of bone marrow cells.

3.2 Preliminary Hypotheses

On the grounds of the above data, the following preliminary hypotheses can be formulated:

1. The expression of ZnT8 in leukocytes in healthy humans decreases with age. Most probably, the same is also true for other tissues. Consequently, the highest expression levels can be observed in childhood. Type 1 diabetes mellitus (DMt1) constitutes the most common autoimmune childhood disease, involving for example: the occurrence of ZnT8 antibodies (ZnT8A) [22]. Higher frequency and levels of ZnT8 expression can predispose to autoimmunity – occurrence of ZnT8A and development of DMt1 – as well as secondary leukocyte dysfunction.
2. In the case of DMt2 (and DMt1) – higher HbA1c levels lead to increased glycation of proteins of SLC transporters with their secondary dysfunction and intercellular zinc accumulation – which stimulates defence mechanisms – for example: increased production of zinc exporters, such as ZnT8. Rising levels of expression of ZnT8 contribute to increased risk of ZnT8A occurrence and autoimmunological inhibition of the compensatory mechanism of zinc excess elimination from cells. From a clinical point of view, it manifests itself in

accelerated progression of organ pathologies accompanying DMt1 and DMt2, as well as escalating dysfunction of the immune system.

3. The single-nucleotide polymorphism (SNP) of zinc transporter 8, its homozygote-heterozygote composition, can impact the level of ZnT8 expression, occurrence of ZnT8A and stimulation of other cells in the immune system. It can also influence the progression of organ pathologies accompanying DMt1 and DMt2, as well as other autoimmunological disorders [23,24].

4. CONCLUSIONS

The variability of ZnT8 expression in leukocytes develops in patients with a genetic predisposition to this condition and it decreases with age. Greater intercellular zinc accumulation may potentially provoke increased levels of its expression, as a support mechanism in zinc homeostasis. The occurrence of ZnT8A may result in leukocyte dysfunction, which is dependent for example, on the level of ZnT8 expression. The same correlation can be observed in non-pancreatic tissues. ZnT8A occur in approximately 16.5% of research participants without any diabetes symptoms and the frequency of their occurrence decreases with age as well [25].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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