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Research on the Role of Ezrin in Glucose and Lipid Metabolism

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Abstract: Ezrin, as a key connecting protein between the cytoskeleton and cell membrane, plays an important role in various cellular physiological processes. In recent years, people have gradually attached importance to its research in the field of glucose and lipid metabolism. Based on relevant research materials, this article elaborates the structure and function of Ezrin, and focuses on its role and potential mechanism in the diseases related to abnormal glucose and lipid metabolism, such as diabetes and its complications, to provide new ideas and theoretical basis for in-depth understanding of the regulation of glucose and lipid metabolism and the prevention and treatment of related diseases.

Keywords: Ezrin; Glucose and lipid metabolism; Insulin signaling pathway

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1. Introduction

Glucose and lipid metabolism is an important process to maintain the normal physiological function of the body, and its imbalance is closely related to the occurrence and development of many diseases, such as diabetes, cardiovascular disease, etc. Ezrin, a protein with important functions in cellular biology, has been found to be associated with glucose and lipid metabolism in recent years [1, 2]. In-depth research on the role of Ezrin in glucose and lipid metabolism is of great significance for revealing the pathogenesis of glucose and lipid metabolism disorders and searching for new therapeutic targets.

2. Structure and function of ezrin

2.1. Structural features

Ezrin is encoded by the VIL2 gene located on human chromosome 6q25.2-q26, which is approximately 24 kb

long and contains 13 exons. This protein is composed of 586 amino acids and has a molecular weight of 81 kDa. Its structure mainly consists of three parts: a highly conserved spherical amino acid terminal (N-terminus) that can be connected to the membrane and bind to cell adhesion molecules (such as ICAM-1, ICAM-2), cell surface transmembrane glycoprotein (CD44), highly glycosylated type I transmembrane glycoprotein (CD43), and other cell adhesion molecules. The middle is an elongated alpha helical structure. The positively charged C-terminal actin binding region contains a threonine residue (Thr567), which is the most important activation site for Ezrin phosphorylation [3, 4].

2.2. Function overview

Ezrin is a connecting protein between the cytoskeleton and cell membrane, which plays a structural and functional regulatory role in the integration and stability of cell membrane regions. It is involved in the formation of microvilli, maintenance of cell morphology, cell movement and adhesion, remodeling of the cytoskeleton, and cellular signal transduction processes. Ezrin acts as a membrane organism and connector in the connection between the cytoskeleton and cell membrane, ensuring effective connection between the cell membrane and cytoskeleton. Meanwhile, studies have shown that Ezrin is closely related to the occurrence, development, and metastasis of tumors, and has always been regarded as a key factor in tumor metastasis [5, 6]. In addition, Ezrin plays an important role in establishing cell polarity and localizing organelles.

3. Ezrin and sugar metabolism

3.1. Study of Ezrin in diabetes

When researchers treated podocytes with high concentrations of glucose, a series of complex molecular events occurred within the cells. The high glucose environment first activates the Smad3 signaling pathway, which acts as the start of a domino effect, leading to a significant increase in Ezrin phosphorylation levels at the Thr567 site. Researchers have accurately detected changes in Ezrin phosphorylation levels through techniques such as protein immunoblotting. Subsequently, the intracellular PKA activity was inhibited, which triggered upregulation of NADPH oxidase 4 expression, leading to a large production of reactive oxygen species (ROS). A large amount of ROS disrupts the redox balance within cells, ultimately leading to podocyte apoptosis. Researchers observed a significant increase in podocyte apoptosis rate using a cell apoptosis detection kit.

In contrast, the situation is completely different in podocytes expressing shRNA-ezrin. Due to the specific interference of shRNA-ezrin on the expression of Ezrin gene, the content of Ezrin in cells is significantly reduced. After high glucose treatment, the apoptosis of these podocytes was significantly reduced. Through TUNEL staining and other methods, it was clearly observed that the number of apoptotic podocytes expressing shRNA-ezrin was significantly lower than that of normal podocytes. At present, the reasons for the difference between these two results are not fully understood. The expression and activation of Ezrin in normal physiological state and high glucose stress state show dynamic changes. How this change accurately regulates downstream signal pathways and the specific role and regulatory mechanism in the complex pathological process of diabetes still need further research.

Under high concentration glucose induction, significant changes were also observed in the mitochondria of renal tubular cells. Researchers used immunofluorescence and protein quantification analysis techniques to find that the expression level of phosphorylated Ezrin (phosphor-ezrin, p-ezrin) in renal tubular cell mitochondria

showed a significant upward trend. At the same time, through ATP detection kits and other methods, it was detected that the intracellular ATP level also increased accordingly. This phenomenon suggests a correlation between phosphorylated Ezrin and mitochondrial dysfunction in renal tubular cells caused by hyperglycemia. As the energy factory of cells, mitochondria dysfunction plays an important role in the occurrence and development of diabetes complications such as diabetes nephropathy. In a hyperglycemic environment, mitochondrial respiratory chain function is impaired, oxidative phosphorylation efficiency is reduced, leading to decreased or abnormal ATP synthesis [7, 8]. The increase of phosphorylated Ezrin may be involved in this pathological process, which changes the location and function of mitochondrial-related proteins by affecting the stability of mitochondrial membrane, thus affecting the energy metabolism and ROS production of mitochondria, and ultimately promoting the development of complications such as diabetes and nephropathy.

3.2. Potential effects of Ezrin on insulin signaling pathway

The insulin signaling pathway is like a precise regulatory network, ensuring the stability of blood sugar. Insulin binds to insulin receptors on the cell membrane and initiates a series of phosphorylation cascades, including phosphorylation of insulin receptor substrates (IRS), which in turn activate downstream signaling molecules such as phosphatidylinositol 3-kinase (PI3K), promoting glucose uptake and metabolism. Although there is currently limited research on the direct effects of Ezrin on the insulin signaling pathway, given its crucial role in cellular signaling transduction, it is speculated that Ezrin may be involved in the regulation of insulin signaling. Ezrin, as a connecting protein between the cytoskeleton and the cell membrane, interacts closely with some receptors and signaling molecules on the cell membrane [9, 10]. It interacts with receptors such as integrins, which may alter the microenvironment of the cell membrane and the spatial conformation of receptors, indirectly affecting the binding affinity between insulin and its receptors. Meanwhile, Ezrin may also interact with some adaptor proteins involved in insulin signal transduction, interfering with the normal assembly and signal transmission sequence between signaling molecules, thereby affecting the insulin signal transduction process. However, these are only speculations based on existing research. In the future, advanced technologies such as gene knockout and protein-protein interactomics need to be used to further explore the specific sites and molecular mechanisms of Ezrin in the insulin signaling pathway, in order to clarify its precise role in maintaining blood glucose homeostasis [11].

4. Ezrin and lipid metabolism

4.1. Functional study of Ezrin in adipocytes

During the process of adipocyte differentiation, the expression level and phosphorylation status of Ezrin show dynamic changes. Researchers tracked changes in Ezrin during the differentiation of adipocytes from mesenchymal stem cells to mature adipocytes using real-time quantitative PCR and protein immunoblotting techniques. In the early stages of differentiation, the expression level of Ezrin gradually increases and reaches its peak in the middle stage of differentiation, and then remains relatively stable in the mature stage. Meanwhile, through phosphorylation-specific antibody detection, it was found that the phosphorylation status of Ezrin at Thr567 site also changed with the differentiation process, and the phosphorylation level significantly increased during the critical differentiation period.

Ezrin may profoundly affect the morphological changes of adipocytes and the distribution of lipid droplets through its interaction with the cytoskeleton. During the differentiation of adipocytes, the cytoskeleton

undergoes rearrangement, and Ezrin acts as a connecting protein that interacts with cytoskeletal components such as actin microfilaments. Research has found that inhibiting the expression or activity of Ezrin can lead to abnormal morphology of adipocytes and disrupted distribution of lipid droplets. Researchers observed through immunofluorescence staining that under normal circumstances, lipid droplets are evenly distributed within cells, but when Ezrin function is restricted, lipid droplets tend to aggregate or disperse unevenly.

In addition, Ezrin may also be involved in regulating the expression of genes related to lipid synthesis and breakdown in adipocytes, thereby affecting the lipid metabolism function of adipocytes. Research has shown that Ezrin can interact with some transcription factors to regulate the expression of key genes such as fatty acid synthase (FAS) and hormone sensitive lipase (HSL). For example, in adipocytes overexpressing Ezrin, FAS gene expression is upregulated, promoting fatty acid synthesis, while HSL gene expression is downregulated, inhibiting fat breakdown and ultimately leading to increased fat storage.

4.2. Ezrin and blood lipid abnormalities and related diseases

Dyslipidemia is an important risk factor for various diseases, such as cardiovascular disease. Some studies have found that Ezrin expression and function are abnormal in animal models or patients with dyslipidemia. In atherosclerotic plaque, the expression level of Ezrin was significantly increased by immunohistochemical staining and quantitative analysis. Further research found that Ezrin may be closely related to the infiltration of inflammatory cells and the formation of foam cells. The infiltration of inflammatory cells, such as monocytes and macrophages, into the vascular wall is one of the initial steps of atherosclerosis. Ezrin may affect the adhesion process between inflammatory cells and vascular endothelial cells by regulating the expression and function of cell adhesion molecules. Research has shown that Ezrin can interact with cell adhesion molecules such as ICAM-1, enhancing its stability and activity on the cell membrane. When the expression of Ezrin is abnormally elevated, inflammatory cells are more likely to adhere and migrate to the lower endothelium of the vascular wall, absorb oxidized low-density lipoprotein (ox-LDL), and gradually transform into foam cells. The formation of a large number of foam cells is a characteristic manifestation of atherosclerosis, and its accumulation further promotes the formation and development of plaque. In addition, Ezrin may also participate in regulating the proliferation and migration of smooth muscle cells and play a role in the remodeling of atherosclerotic plaque, but the specific mechanism remains to be further studied.

5. Conclusion

In summary, Ezrin, as a key protein connecting the cytoskeleton and cell membrane, plays an important role in various cellular processes related to glucose and lipid metabolism. In diabetes and its complications, the expression and phosphorylation of Ezrin are closely related to apoptosis and mitochondrial dysfunction. In terms of lipid metabolism, Ezrin participates in the differentiation and functional regulation of adipocytes, and is associated with the occurrence and development of dyslipidemia and related diseases such as atherosclerosis. Furthermore, Ezrin may play a bridging role in the interrelationships of glucose and lipid metabolism. However, there are still many shortcomings in the current research on the role of Ezrin in glucose and lipid metabolism. For example, the specific molecular mechanisms by which Ezrin participates in glucose and lipid metabolism in different cell types are not yet fully understood. The interaction between Ezrin and other signaling pathways related to glucose and lipid metabolism needs further investigation. The development of drugs or therapeutic strategies targeting Ezrin to

regulate glucose and lipid metabolism is still in the exploratory stage. Future research requires the comprehensive use of various techniques such as cell biology, molecular biology, genetics, etc., to deeply study the mechanism of Ezrin in glucose and lipid metabolism and provide new targets and strategies for the prevention and treatment of diseases related to glucose and lipid metabolism disorders.

Disclosure statement

The authors declare no conflict of interest.

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