Clinical Application of SIRT1 for Diabetes Therapy

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SIRT1, also known as NAD-dependent deacetylase sirtuin-1, is a protein that in humans is encoded by the SIRT1 gene [1]. Moreover, as a member of the sirtuin family of proteins, homologs of the Sir2 gene in S. cerevisiae, SIRT1 plays an important role in extension of the cell cycle, transcriptional silencing, chromatin homeostasis, DNA damage repair and so on [2]. Recently, many studies demonstrated that SIRT1 is a versatile transcriptional regulator, can deacetylate a variety of transcription factors, such as the FOXO, PGC1-a, p53 and PPAR-γ that control metabolism and endocrine signals, and adjust its biological activities [3]. In addition, through regulating the balance of energy metabolism, SIRT1 are widely involved in glucose and lipid metabolism, insulin secretion and other metabolic pathways, so it can maintain a steady state of the body’s glucose and lipid metabolism [4].

As we all know, diabetes is a disease because of lack of insulin secretion or insulin resistance [5]. The main reason for the absolute lack of secretion of insulin is that defection of insulin β-cell for its playing a major important role in the development of type I diabetes [6]. In order to further verify the fact, studies have shown that the majority of genes related to identified types of diabetes have a great relationship with the functional defection of β-cell [7]. Besides these, it is more important that SIRT1 may be able to restore the function of β-cell and thereby increase the insulin secretion [8]. So, we can draw a conclusion that SIRT1 may be in contact with diabetes closely.

In order to further clarify its mechanism, many studies verify that SIRT1 with different substrates such as the FOXO, PGC1-a, p53, and PPAR-γ, play a tissue-specific effects together and activation of the SIRT1 may cause: (1) inhibition of p53 activity, thus inhibiting the pancreatic β cell aging and apoptosis, meanwhile extending the life of islet β cells; (2) inhibiting the activity of FOXO and enhancing the INS/IGF-1 signaling pathway, thereby improving the insulin sensitivity and reducing β-cell apoptosis, and at last slowing the aging of β-cells; (3) inhibiting the transcriptional activity of PPAR-γ, thus inhibiting the formation of fat cells and fat accumulation; (4) deacetylating the PGC1-a and thus inhibiting the gluconeogenesis to maintain glucose and lipid balance; (5) down-regulating the NF-kB activity, thereby preventing the formation of fatty liver and improving the insulin sensitivity. Thus, researchers have to pay attention to the SIRT1 on the endocrine and metabolic regulation, especially the relationship between SIRT1 and diabetes [9]. More and more evidence suggest that SIRT1 is a significant clinical therapeutic potential target for diabetes. In addition, it is a good measure for the prevention and treatment of diabetes through the activation of SIRT1 [10].

In order to further understand all the action effect of SIRT1 in mammals, especially the role played in the development of diabetes, it is necessary to design and produce gene knock-out transgenic mice, and thus provides deep insight into the SIRT1’s biological function and effect [11]. Meanwhile, it is important and necessary to make up for the clinical data and provide direct evidence from clinical patients on the basis of relationship between SIRT1 and diabetes. In addition, in order to better understand the regulating mechanisms and signaling pathways of SIRT1, it is crucial to verify and prove the new substrate effect of SIRT1 protein substrates. Besides these, it is most important to confirm the SIRT1 as a drug targeting through continued development of small molecule agonist biological activity for pharmacology [12].

So, it will provide a good new idea to deeply understand the development process of its regulation of diabetes because of the complexity and contradictions of SIRT1 on the endocrine and metabolic signals regulating it. Furthermore, with the constant awareness of the SIRT1 biological effect, it will contribute to the endocrine and metabolic diseases treatment with the SIRT1 as targeted.

References


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