Advances in diabetic microvascular complications and related molecular mechanisms

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ABSTRACT

With the change of production and life style, the change of dietary structure and the aggravation of population aging, the incidence and fatality rate of diabetes mellitus have been increasing year by year. The pathogenesis of diabetes varies and is closely related to many factors, such as genetic factors, environmental factors, eating habits and so on. Those that endanger the life quality and survival of diabetic patients are mostly complications, including various macrovascular complications and microvascular complications, such as diabetic cardiomyopathy, diabetic nephropathy, diabetic encephalopathy and diabetic foot. The related molecular mechanisms of the pathogenesis of diabetic nephropathy, diabetic retinopathy and diabetic foot are discussed in this paper to provide reference for new drug research and clinical treatment.

1. Introduction

With the changes of production and lifestyle, the changes of diet structure and the intensification of population aging, the incidence, disability and mortality of diabetes have been rising year by year. Diabetes, hypertension and malignant tumor have become the three major threats to human health and survival. The main clinical manifestation of diabetic patients is hyperglycemia, which is accompanied by polydipsia, polyphagia, diuresis and body wasting. Diabetes is divided into type I diabetes and type II diabetes according to the different states of insufficient insulin secretion or insulin resistance[1,2].

The incidence of diabetes is closely related to genetic, environmental, dietary and other factors. It has been reported that both type I and type II diabetes have obvious familial tendency[3]. Meanwhile, the genetic genes of type 2 diabetes mellitus include insulin as well as its receptor gene, leptin gene, glucokinase gene, mitochondrial gene and so on. Diabetic patients are mainly manifested in abnormal carbohydrate, lipid and protein metabolism, belonging to the category of metabolic syndrome. Those endangering the life quality and living state of patients with diabetes are mostly its complications, which involve a variety of macrovascular complications and microvascular complications, such as diabetic cardiomyopathy, diabetic nephropathy, diabetic encephalopathy and diabetic foot[4]. In this part, the molecular mechanisms of diabetes and its microvascular complications are reviewed to provide reference for the new drug development and clinical treatment.

2. Diabetic microvascular complication: retinopathy

Diabetic retinopathy is the most common and serious microvascular complication in diabetic patients, and has become one of the important causes of blindness in clinical patients. Diabetic retinopathy has become an important factor affecting patients’ quality of life. At present, systematic study has been carried out on retinopathy and the molecular mechanism of its pathogenesis has been analyzed. The study that analyzes the
protective effect of Puredan Superfine Powder on retinopathy of rats with diabetes mellitus induced by streptozotocin and its influence in NF-κB signaling pathway shows that PRD may exert protective effect on diabetic rats' retinas by specifically blocking AGEs/RAGE/NF-κB signaling pathway[5]. Previous research has also confirmed that Shuangdan Mingmu Capsule can regulate the Ras-Raf-1-MEK-ERK pathway to treat DR[6], and CTGF may exogenously regulate the balance with vascular endothelial growth factor (VEGF) level to effectively slow retinal fibrosis progression[7]. WANG Chenghui and others[8] have also found that reducing TLR4 levels could improve obesity and insulin resistance in patients with type 2 diabetes mellitus, and targeted inhibition of TLR4 might be a potential target for the treatment of type 2 diabetes and its chronic complications. The study that analyzes the mechanism of PD1/PDL1 signaling pathway in the treatment of proliferative diabetic retinopathy with Damingyin has confirmed that Chinese traditional medicine Damingyin preparation can improve the visual acuity level in patients with proliferative diabetic retinal complications, and the process may be realized through inhibiting PD1/PD-L1 signal transduction protein expression and activation to restore the function of mononuclear cells, make the mononuclear cells mainly inhibit inflammation and restrain the expression of related inflammatory markers[9]. The study that analyzes the protective effects and mechanism of SIRT1 for the regulation of p38 MAPK pathway on retinal ganglion cells in rats with diabetic retinopathy has also found that in diabetic retinopathy model, SIRT1 expression is up-regulated, it inhibits the apoptosis of RGCs and protects the RGCs of diabetic retinopathy, and the anti-apoptotic mechanisms may be related to its inhibition on p38 MAPK expression[10].

Although the molecular mechanism of diabetic retinopathy has been extensively studied, the underlying cause of diabetic retinopathy has not been fully elucidated at present. Diabetic retinopathy (the most common microvascular complication) is the main cause of blindness in diabetic patients, and taking intervention as soon as possible is particularly important for development of retinopathy and reduction of blindness rate.

3. Diabetic renal dysfunction and diabetic nephropathy

Diabetic nephropathy is the main and most common microvascular complication in diabetic patients in later stages. Diabetic nephropathy has become the most common clinical cause of end-stage renal disease. The increasing incidence of diabetes leads to the obviously increasing number of diabetic nephropathy patients. Diabetes can be divided into type I diabetes and type II diabetes according to the different responses to insulin: the proportion of diabetic nephropathy (microvascular complication) in patients with type I diabetes is about 35%, while the rate of diabetic nephropathy (microvascular complication) in patients with type II diabetes is about 22%. The study that polydatin protects diabetic nephropathy rats from renal inflammation by regulating the TLR4/NF-κB signal pathway shows that polydatin has obvious protective effect on the renal inflammation caused by diabetic nephropathy, and its mechanism may be related to regulating TLR4/NF-κB signaling pathways and reducing inflammatory factor contents in the kidney tissue to exert anti-inflammatory protective effect[11]. The study that analyzes the effects of combined saxagliptin therapy on inflammatory cytokines and mononuclear cell PI3K-Akt pathway in elderly diabetic nephropathy has also confirmed the saxagliptin treatment can significantly reduce the Hb A1c, 24 h UPro and Cr in elderly patients with diabetic nephropathy to improve renal function, it can also reduce the peripheral blood TNF-α, IL-6 and IL-1β levels, relieve peripheral inflammatory immune response and significantly increase the PI3K and Akt phosphorylation levels in peripheral blood mononuclear cells, and saxagliptin improves peripheral blood hyperglycemic state, further recovers PI3K/Akt phosphorylation activation level and participates in inhibiting inflammatory reactions[12], LIU Junfen and others[13] have also confirmed that the activation of TGF-β/Smad signaling pathway and p38MAPK signaling pathway in diabetic nephropathy patients may be one of the main causes of renal inflammation. The increased level of urinary o 1-MG is a direct manifestation of renal glomerular damage, and the above indicators can be used as the monitoring indicators of severe microvascular disease in diabetic patients. The study that polydatin protects diabetic nephropathy rats from renal inflammation by regulating the TLR4/NF-κB signal pathway has also shown that polydatin has a significant protective effect on kidney inflammation caused by diabetic nephropathy, and its related mechanism may be regulating the TLR4/NF-κB signaling pathways and reducing inflammatory factor contents in kidney tissue to achieve anti-inflammatory protective effect[14]. Previous research has also found that AQP5 may participate in the pathological process of the occurrence, development and deterioration of diabetic nephropathy, AC-α AMP-PKA pathways show obvious negative regulation on aquaporins 5 in renal tissues[15], and Danggui Buxue Decoction can inhibit IRE1α -JN pathway-related protein expression in the kidney tissue under high glucose and reduce endoplasmic reticulum stress-related protein molecule expression level in the kidney under high glucose to protect kidney tissue[16]. Previous research has also confirmed that rheic acid can regulate the expression of p-JNK and PPAR γ to improve insulin resistance, inhibit renal mesangial cell apoptosis and protect the kidney[17], and the classic signal transduction pathway and the trans-signal transduction pathway mediated by IL-6 are proven to be involved in the pathogenesis of DN through IL-6 receptor and soluble IL-6 receptor respectively[18]. TONG Nan and others[19] have also found that traditional Chinese medicine Yishen Granules may alleviate renal pathological changes in diabetic nephropathy rats by regulating PI3k/Akt/m TOR and LKB1/AMPK/Sirt1 signaling pathways.

The pathogenesis of diabetic nephropathy may be related to a variety of signaling pathways in cells, and a particular signaling
pathway may be involved in regulating one or several targets[20].

Therefore, multi-signal pathways should be analyzed in vivo and in vitro to provide references for further elucidating the pathogenesis of diabetic nephropathy.

4. Diabetic foot

Diabetic foot is the lower limb infection ulcer and deep tissue destruction of diabetic patients due to the combination of neurological disease and various peripheral vascular lesions of different degrees. Diabetic foot is a systemic disease, which is not only manifested as the surgical symptoms such as limb ulceration and bacterial infection, but also the clinical manifestations of internal diseases. Diabetic foot is a severe stage in diabetes development, which seriously threatens the patients' health and is one of the main causes of disability and death of patients.

The treatment of diabetic foot is usually by ulcer treatment, infection treatment and Charcot joint treatment, but the effect is usually not ideal. Therefore, the analysis of the molecular mechanism of diabetic foot disease has important practical significance for early prevention and treatment. In the study that investigates the mechanism of Shengji Xiangpi Paste in promoting ulcer healing in diabetic rats from the bFGF/Akt/Caspase pathway, it was found that Shengji Xiangpi Paste could promote the healing of diabetic wounds through the bFGF/Akt/Caspase pathway[21].

Previous research has also confirmed that the down-regulation of Wnt/β-catenin pathway could lead to the pathological refractory ulcer in patients with diabetes mellitus, Simiaoyong’an decoction can also regulate the Wnt/β-catenin signaling pathway-related protein molecule levels to promote the healing effect of diabetes ulcer (such as diabetic foot) effect[22], and MEBT/MEBO may dynamically regulate vascular transformation factor β 1 and P-smad3 protein molecule expression levels to promote the healing effect of diabetic foot ulcer in diabetic patients[23]. The study that analyzes the influence of Tongxinluo Combined With Peripheral Blood Derived Mesenchymal Stem Cells Transplantation on the Angiogenesis Through PI3K/Akt Signal Pathway of Diabetic Foot Rats has also found that Tongxinluo combined with peripheral blood mesenchymal stem cell transplantation can regulate the PI3K/Akt signal pathway and promote endothelial cell proliferation and differentiation so as to promote the angiogenesis in diabetic foot rats[24]. XU Jienan and others[25] have also proved that Yiqi Huayu Recipe could promote angiogenesis of diabetic refractory wounds and accelerate wound repair and healing by regulating AGES/RAGE/NF-κ B signaling pathway. The study that analyzes the treatment effect of Tongxinluo combined peripheral blood derived mesenchymal stem cells transplantation on angiogenesis of HIF-1/VEGF pathway and miR-210 in diabetic foot rats has also revealed that Tongxinluo combined with peripheral blood mesenchymal stem cell transplantation may promote endothelial cell proliferation and differentiation and promote angiogenesis by regulating HIF-1/VEGF pathway and mi R-210 expression[26]. In the study that analyzes the expression changes of Wnt/β-catenin signaling pathway in diabetic ulcer, it is also confirmed that the down-regulation of Wnt/β-catenin pathway may lead to the refractory diabetic ulcer, and the down-regulation of this pathway may be caused by the decline of Rsps-3 protein expression[27].

Diabetic foot is the most common microvascular disease of diabetes, but the current treatment measures are not satisfactory. Therefore, the pathogenesis of diabetic foot should be constantly explored, related pathogenesis factors and molecular mechanism should be actively controlled, and prevention should be given priority to, so as to fundamentally reduce the risk of diabetic foot.

5. Summary

The incidence and disability rates of diabetes are increasingly severe with the intensification of diet structure and population aging[28]. The occurrence of microvascular complications in diabetic patients has become a major threat to their health and survival. Diabetic nephropathy, diabetic foot and diabetic retinopathy are the most common and severe diabetic microvascular complications in clinical patients at present. Though the molecular mechanisms of the occurrence and development of diabetic microvascular complications have been analyzed in this review, it should be pointed out that the occurrence of diabetes and its microvascular complications is not the result of single signal pathway. In the future, the study should be carried out from different pathological models, in vivo and in vitro, etc., so as to provide references for more accurate understanding of the pathogenesis of diabetic microvascular complications.

References


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