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Exploring the role of the TLR4/NF-κB signaling pathway in diabetic retinopathy

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Abstract. Diabetes mellitus (DM) is a major cause of blindness and the neurodegenerative and microvascular disease known as diabetic retinopathy (DR). Diabetes-related retinal neurodegeneration (DRN) is thought to be a potential therapeutic target for primary or secondary prevention of traditional DR while the exact nature of the link between DRN and diabetic retinal vasculopathy (DRV) is still unknown. Therefore, compared with the DRV, in-depth study of DRN may provide a better understanding of this important cause of blindness. Immunoinflammatory mechanisms are currently believed to play crucial role in the occurrence and development of DR. Interrelated molecular pathways, such as the formation of glycosylation end products and oxidative stress (OS) in late diabetes, contribute to the inflammatory response. Furthermore, blocking the TLR4/NF-κB signaling pathway has been shown to be an effective way to reduce DR, as demonstrated by a number of studies. This paper examines the function of the inflammatory response and TLR4/NF-κB signaling pathway in the pathophysiology of DRN, which may offer fresh perspectives on DR therapy.

Keywords: Diabetic Retinopathy, Retinal Microglia, Inflammation.

1. Introduction

As a microvascular consequence of DM, adult-onset visual impairment and blindness are primarily caused by DR. The development of retinal glial cells and microangiopathy and neurodegeneration are the cause of DR, which is not exclusively a microangiopathic condition, according to research [1]. The apoptosis of neuronal cells causes diabetic retinal neurodegeneration (DRN), which is characterized by neuronal damage and glial cell proliferation. Visual loss caused by DR is irreversible. One of the earliest and most widely distributed types of retinal neurons is the retinal ganglion cell (RGC). RGCs have a high sensitivity to pathological damage and are crucial in the conversion, transmission, and processing of visual information because they are physiologically responsible for sustaining sharp central vision. Therefore, the retina can be permanently damaged in various systemic diseases, such as diabetes, when axonal damage occurs in RGCs. Retinal microglia are local immune cells that live in the retina. Chronic inflammatory responses caused by high glucose long-term can result in the release of a variety of inflammatory factors, alteration of Müller cell glialization, disruption of the blood-retinal barrier (BRB) structure, and increase neuronal apoptosis. Currently, a growing body of research indicates the value of microglia in the occurrence of DR. TLR4, as a mediator of immune-inflammatory response, has also received more and more attention because it can activate the NF-κB signaling pathway when it is

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expressed in the retina, leading to a series of changes in the retinal microvascular abnormalities and nerve damage in DR.

Understanding the pathophysiologic mechanisms of nerve injury in DR is essential for comprehensive clinical treatment of DR. In this paper, the mechanism of the TLR4/NF-κB signaling pathway's participation in DR is reviewed, and research advances based on investigating the link between the NF-κB signaling pathway and microglia activation are made.

2. NF-κB signaling pathway

2.1. Basic concepts of TLR4

The activation of toll-like receptors (TLRs) which a type of pattern recognition receptors, is caused by damage-associated molecular patterns (DAMP) and pathogen-associated molecular patterns (PAMP).

TLR4 is the TLR that was discovered first and studied extensively, being more prevalent and expressing in photoreceptors, astrocytes, microglia, retinal vascular endothelial cells, and retinal pigment epithelium. TLR4, an immune-inflammatory response mediator, can mediate the inflammatory response when expressed in the retina by triggering the NF-κB signaling pathway. This pathway is intimately linked to a number of alterations, including microvascular abnormalities in the retina and neurological impairment in diabetes [2].

2.2. Activation of the TLR4/NF-κB signaling pathway and microglia activation

Large levels of glycosylation end products (AGE) have accumulated in the late diabetes cycle; consequently, NADPH oxidase (PHOX) is activated in the AGE-RAGE axis, bringing about the generation of reactive oxygen species (ROS). NF-κB is an important nuclear transcription factor, regulating inflammation and expression of genes related to innate response. The TLR4/NF-κB pathway is activated by increased intracellular ROS, leading to a notable increase in TLR-4 expression. This consequently initiates the phosphorylation of NF-κB and increases the expression of RAGE genes in retinal neurons [3]. After activation, NF-κB translocates to the nucleus, where modifies the transcriptional control of proinflammatory genes. Activation and nuclear translocation of NF-κB are critical processes in the activation of microglia. Microglia will then produce huge amounts of proinflammatory cytokines through expression.

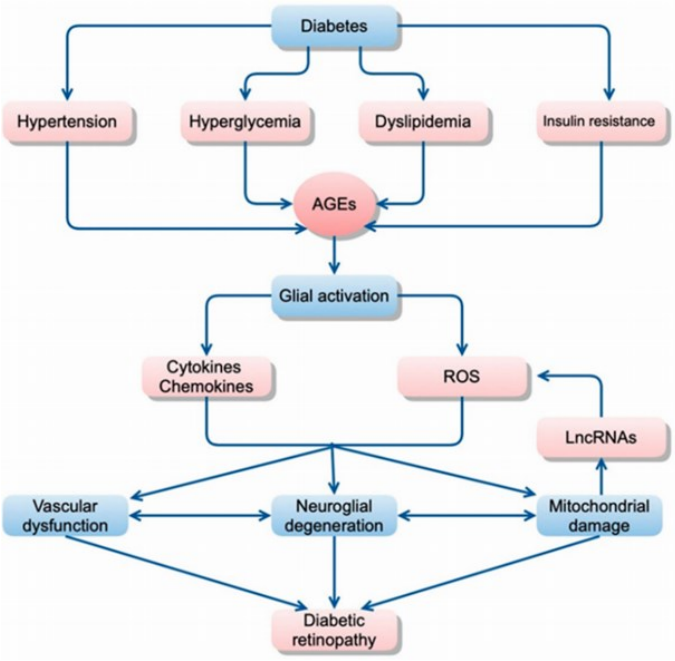

Figure 1. Things that either directly or indirectly cause inflammation to rise.

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A potential pathophysiological setting for DR is depicted in Figure 1. Hyperglycemia, dyslipidemia, and insulin resistance are examples of metabolic abnormalities that result in neuroglial dysfunction. This dysfunction causes inflammation, aberrant trophic factor signaling, and disruption of metabolism, all of which cause neuronal apoptosis. AGE accumulation may be a major factor in DR inflammation, presumably because AGE accumulation may be mistaken for foreign objects by immune-stimulating cells, which can promote retinal inflammation.

3. Microglia accelerate optic nerve damage

3.1. Basic concepts of microglia

Consistent glial cell function, particularly that of microglia, is necessary to sustain neuronal activity within the central nervous system. Progenitor cells of mesodermal/mesenchymal origin are the source of microglia, which are constantly monitoring their environment and quickly becoming activated in response to stress, injury to the brain, and changes in neurochemistry. As immune cells that live in the brain, immune surveillance is the responsibility of microglia, which also respond quickly to changes or challenges in the microenvironment. Therefore, the number of microglia increases under high glucose environments, and microglia are considered as the first detector of hyperglycemic signals in diabetic patients [4].

Numerous disorders and developmental processes in the central nervous system (CNS), including neuronal migration, synaptogenesis, and neuroplasticity, are linked to various substances released by activated microglia. Importantly, interactions between neurons and glial cells have a major function in the CNS's ability to operate. Overactive microglia can release effectors in an uncontrollable manner, which can lead to increased OS and nerve inflammation. As a result, additional undesirable effectors are released, continually escalating neurotoxicity and ultimately culminating in neuronal death.

Thus, extensive activation of microglia is linked to the pathophysiology of many neurodegenerative disorders because of their immunological activity. Common characteristics of these neuropathies include neuroinflammation and microglia activation.

3.2. Microglia produce respiratory depression on the optic nerve

Damage to the mitochondria brought on by apoptosis is one of the reasons retinal cells die in DR patients. As a result, non-coding RNAs (mt-ncRNAs) are upregulated [5]. Long chain non-coding RNAs (lncRNAs) for instance lncMALAT1 and lncNEAT1, have been found to be more highly expressed in the bloodstream in diabetic individuals. Large amounts of nitric oxide (NO) are produced when microglia are activated. NO competes with oxygen to inhibit mitochondrial respiration in optic neurons through reversible binding to cytochrome oxidase. This results in a decrease in energy production, hypoxic sensitization, and excitotoxicity, which is a cytotoxic state brought on by excitatory amino acids like glutamate overstimulating neuronal NMDA receptors. Furthermore, by preventing mitochondrial respiration, nitric oxide derivatives including S-nitrosothiols, nitrogen dioxide (NO_2), peroxynitrite ($ONOO^-$), and nitrogen trioxide (N_2O_3) can also be harmful to the visual nerve [6].

3.3. Microglia cause oxidative stress in the optic nerve

The membrane NADPH oxidase compound in microglia produces superoxide, and peroxisomes, mitochondrial electron transport, and xanthine oxidase produce intracellular ROS. The resulting consequence is known as OS. RGCs are a particular type of projection neuron found in the retina's inner layer. These neurons are one of the key cell types that influence optic neuropathy, including DR and glaucoma. They can transfer visual information in the form of action potentials from the retina to certain brain regions. Superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radicals (-OH) are products of ROS that are produced excessively in OS, which is hypothesized to be the cause of many ocular neurodegenerative diseases, including DR, glaucoma, and retinal ischemia-reperfusion injury. In these disorders, the death of RGCs is believed to be caused by this stress. The body's synthesis of ROS and biological antioxidants' capacity to scavenge oxidants and reverse the effects of OS are in balance

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under normal circumstances. OS and subsequent cellular damage, such as lipid peroxidation in cellular membranes and oxidative damage to proteins and DNA, can be caused by an excess of ROS or by the malfunction of antioxidant enzymes. Therefore, loss of RGCs can result from OS in a number of ocular neurodegenerative illnesses, and RGC destruction is a key pathogenic characteristic of DRN.

An essential part of the pathophysiology of DRN is OS. Hyperglycemia activates various metabolic pathways such as glycolysis, advanced AGE, protein kinase C, hexose amine and other metabolic pathways, which can increase ROS and cause cellular OS damage [7]. The expression of pro-inflammatory genes, such as NF-κB, may increase with OS, which can lead to significant production of pro-inflammatory molecules. In the initial phases of DR, there was an elevation in activated microglia of both the pro-inflammatory (M1) and anti-inflammatory (M2) types. The fraction of M1 is substantially higher than that of M2, and the ratio of M1/M2 grows as the condition worsens [8]. One of the key neurotoxic mediators of neuroinflammation, M1 secretes pro-inflammatory molecules that cause damage to neurons and even death, including interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF-α), and chemokines [9]; these pro-inflammatory factors are involved in the localization of retinal no-perfusion area and neovascularization, exacerbating BRB dysfunction and promoting vascular leakage and peri-endothelial cell apoptosis [10]; at the same time, pro-inflammatory factors can cause activation of the apoptotic protein Caspase-3, which promotes retinal neuronal death [11]. Besides, increasing the TNF-α levels in microglia modifies the excitability of neurons and glutamatergic transmission by disrupting the calcium homeostasis of neurons and decreasing the glutamate uptake of astrocytes. This leads to excitotoxicity and prevents synaptic development [12].

A high-glucose environment can cause changes in various components of the retinal neurovascular unit, and microglia interact with these components and participate in the development of DR. Consequently, focusing on microglia as a target therapy for DR has drawn a lot of interest lately.

4. Conclusion

The TLR4/NF-κB signaling system, which can be suppressed to lessen retinal inflammatory reactions and nerve damage, is primarily responsible for the development of DR. In the present study, we discovered that significantly elevated TLR-4 expression initiated intracellular signaling pathways that initiate NF-κB nuclear translocation, hence promoting the release of pro-inflammatory cytokines TNF-α and IL-8. This process destroys RGCs and amplifies the inflammatory response, exacerbating DR.

Although a great deal of progress has been made in recent years in clinical research aimed at preventing DR by selectively regulating TLR4/NF-κB signaling channels, our knowledge of the TLR4 signaling pathway's role in DR is still limited. In-depth study to elaborate the influence of TLR4/NF-κB signaling pathway in DR and its specific regulatory mechanism is of great significance, which not only can provide theoretical and data support for the prevention and treatment of DR, but also can be expected to discover more new ideas for the management of DR from an inflammatory mechanisms standpoint.

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