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Review

The role of SIRT1 in diabetic retinopathy

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ABSTRACT

The prevalence of diabetes mellitus (DM), has been increasing worldwide. Diabetic retinopathy (DR) is the most common microvascular complication in diabetes. It is a multifactorial disease that occurs primarily through the long-term detrimental effects of hyperglycemia. The pathogenesis of DR is complex, including inflammation, oxidative stress and advanced glycation end products (AGES).

SIRT1 is a nicotinamide adenosine dinucleotide (NAD+)-dependent deacetylase that removes acetyl groups from proteins which can be implicated in DR. Inhibition of miRNAs such as miR-23b- 3P and miR-34a and activation of adenosine monophosphate-activated protein kinas (AMPK) and Peroxisome proliferative-activated receptor α (PPARα), modulate inflammation by enhancing the level of SIRT1. SIRT1 activation leads to the down regulation of nuclear factor kappa-light-chain-enhancer of activated of B cells (NF-κB), and the downstream pathway including increased level of Interleukin-17 (IL-17) and other pro-inflammatory cytokines. Oxidative stress- induced apoptosis is due to activation of some transcriptional factors such as p53 and Protein arginine methyl transferase 1 (PRMIT1) which are inhibited by SIRT1. In addition to these, the increased level of some transcriptional factors such as, vascular endothelial growth factor (VEGF), hypoxia − induced factors (HIFs), transforming growth factor β1 (TGF-β1), endothelin-1 (ET-1), fork head box O 1 (FOXO1) and Notch signaling may be inhibited by activation of SIRT1 leads to attenuation of vascular dysfunction.

In conclusion, SIRT1 regulates apoptosis, inflammation and oxidative stress resulting in improving DR. This review focuses on the role of SIRT1 in DR.

1. Introduction

1.1. Sirtuins

Silent information regulator 2 (SIR2) proteins- sirtuins- are a family of histone deacetylases (HDACS) that catalyze deacetylation of both histone and none histone lysine residues. They have a range of molecular function and emerged as important proteins in ageing, inflammation, stress resistance and metabolic regulations [1]. In mammals, there are 7 homologues of SIR 2 termed sirtuins (SIRT1-SIRT7). SIRT1 was the first family member to be discovered and is still the most studied [2]. It needs cellular nicotinamide adenosine dinucleotide (NAD+) as a cofactor for deacetylation reactivity. Nicotinamide is liberated from NAD+, generating the novel metabolite o – acetyl-ADP-ribose [3]. SIRT1 is found in nucleus and cytoplasm and is considered as a potential target for the treatment of human pathologies such as diabetic retinopathy (DR) [2] (Fig. 1).

1.2. Diabetes

Diabetes mellitus (DM) is one of the major health threats in the modern societies. The incidence and prevalence of diabetes mellitus have significantly increased worldwide in recent decades. It is also the most common lifestyle disorder in the developed and developing countries [2]. DM is a multifactorial disease which is characterized by impaired glucose homeostasis, reduced insulin activity and insulin resistance leading to elevated blood glucose [4]. Type 1 DM results from failure of the pancreas to produce enough insulin. Type 2 DM begins

Abbreviations: SIR2, Silent Information Regulator2; HDACs, histone deacetylaser; NAD+, nicotinamide adenine dinucleotide; DM, diabetes mellitus); AGEs, advanced glycation end products; AMPK, adenosine monophosphate-activated protein kinas; TGFβ1, transforming growth factor β1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated of B cells; MMP-9, matrix metalloproteinase9; NO, nitric oxide; RECS, retinal endothelial cells; TNF, tumor necrosis factor; ET-1, endothelin-1; PPARα, Peroxisome proliferative-activated receptor α; ECM, extra cellular matrix; FN, fibronectin; ICAM, intracellular adhesion molecule; NAMPT, nicotinamide phosphoribosyl transferase; GLP-1, glucagon -like -peptide -1; RPE, retinal pigment epithelial; NICD, notch 1 intracellular domain; HIFs, hypoxia – induced factors; Th, T helper; PRMT1, protein arginine methyl transferase1; PRMCs, peripheral blood mononuclear cells; mnSOD, manganese superoxide dismutase; GFAP, glial fibrillary acidic; VEGF, vascular endothelial growth factor; FOXO, fork head box O

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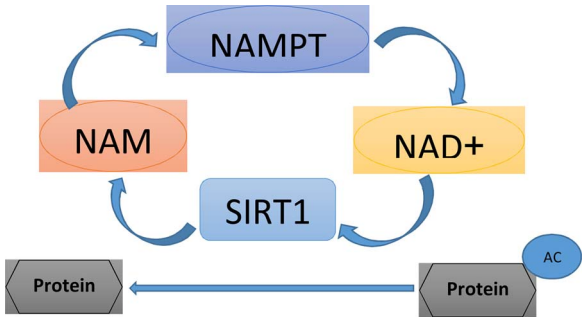

Fig. 1. Cellular nicotinamide adenosine dinucleotide (NAD+) needed as a cofactor for deacetylation reaction catalyzed by sirt1. Nicotinamide phosphoribosyl transferase (NAMPT), an enzyme that catalyze NAD+ synthesis from nicotinamide: sirt1 acts by removing acetyl groups from proteins in the presence of NAD+.

with insulin resistance, a condition in which cells fail to respond to insulin property. Hyperglycemia causes structural and functional alteration to vascular system thus affecting the target organs [2].

1.3. Diabetic retinopathy

Diabetic retinopathy (DR) is the most common microvascular complication in diabetes. It is a multifactorial, debilitating disease that occurs primarily through the long- term detrimental effects of hyperglycemia [5]. DR affect neurons, glial cells and vascular element of the retina. In fact, the endothelial cells of retinal micro- vessels undergo alteration in the expression of various genes in response to hyperglycemia. This results in activation of several transcription factors, lead to loss of blood retinal barrier (BRB) integrity, retinal microvascular occlusion and ischemic retinal changes. The vision loss associated with DR has been shown to decrease patient quality of life. A major challenge in threating DR, is the molecular and pathological features resulting from high glucose and maintained despite subsequent effects [4]. The pathogenesis of DR is complex, including inflammation, oxidative stress and advanced glycation end products (AGEs) [6]. Inflammations is a major contributing factor in the development of diabetic microvascular complications [7]. Inflammatory process, includes leukocyte adhesion and the cytokine network which triggers vascular hyper permeability. Retinopathy is characterized by an initial phase of vessel loss leading to tissue ischemia and hypoxia followed by sight threatening pathologic neovascularization in the second phase. Retina is vulnerable to oxidative stress and hyperglycemia. Inflammation could significantly increase production of reactive oxygen species (ROS), which in turn aggravates retinal neuron damage and cause apoptosis. This is further supported by the fact that antioxidant could preserve retinal neurons in diabetes [4]. In this review, we focus on the role of SIRT1 in diabetic retinopathy (Fig. 2).

1.3.1. PPARα/SIRT1/NF-κB

Nuclear-factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a master regulator of various genes involved in inflammation and apoptosis through increased binding of NF-κB to these genes [8].

Activation of NF-κB was shown to promote expression of pro-inflammatory cytokines and various pro- apoptotic regulators in retinal endothelial cells (RECS) [9]. Muller cells are a major source of this pro-inflammatory factors. The gene transcribed by NF-κB will modulate tumor necrosis factor (TNF)-α, interleukin(IL)-8 and IL-6 expression, thus helping the initiation of inflammatory responses [7]. Under physiological conditions, there is a balance between the histone acetylation and deacetylation of NF-κB [10]. Hyperglycemia lowered the level of intracellular NAD+, and reduced the expression of SIRT1. SIRT1 inhibits NF-κB transcription by directly deacetylating the Rela/P65 protein at lysine 310 [9].

Peroxisome proliferative-activated receptor α (PPARα) is a nuclear

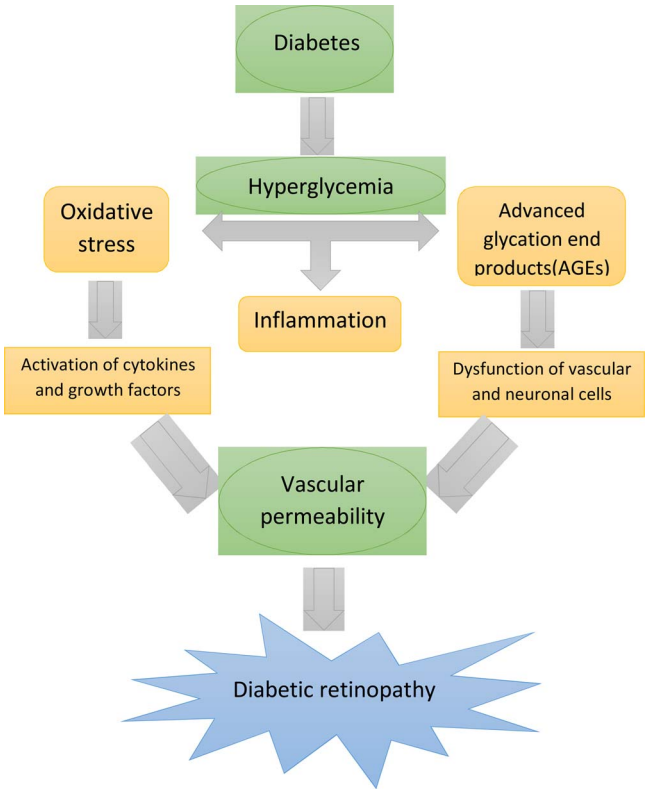

Fig. 2. Diabetes-induced hyperglycemia cause diabetic retinopathy (DR). The pathological cause of DR is complex, including inflammation, oxidative stress and advanced glycation end products (AGEs). These pathways triggers vascular permeability and leads to DR.

receptor protein in humans that is encoded by the PPARα gene. Hyperglycemia reduced PPARα expression, followed by inactivating SIRT1 caused a significant increase in the level of NF-κB expression leading to inflammation and apoptosis. Therefore, PPARα upregulates SIRT1 expression and activity [11]. SIRT1 suppresses NF-κB signaling and results in the reduction of the inflammatory responses in endothelial cells and also inhibits the apoptosis [9].

In conclusion, PPARα/SIRT1/NF-κB may be a commonly used signaling pathway during the DR [11].

1.3.2. SIRT1/VEGF

Muller cells are the predominant glial cells in the retina. They monitor the retinal structure and functions [12]. In diabetes, the Muller cells produce pro – inflammatory cytokines to restore the retinal homeostasis [7]. Up regulation of glial fibrillary acidic (GFAP) and vascular endothelial growth factor (VEGF) leading to a glial reaction and blood barrier hyper-permeability [13].

In an ischemic retina, the induction of VEGF expression mediated the pathological interocular proliferation of vessels [6]. Although induction of endogenous SIRT1 in ischemic retina is critical under stress condition to protect against retinopathy, over expression of SIRT1 does not offer additional protection in retinopathy [14].

SIRT1 activity improves through modulation of the NOX 4/NADPH oxidative subunit, thus reduces reactive oxygen species (ROS) formation. This process leads to the deacetylation of lysine 310- p65, which down regulates the expression of VEGF and GFAP proteins [15].

1.3.3. Micro RNA/SIRT1/NF-κB

Micro RNA (mi RNAs) involve in many biological process, including the development of metabolic diseases such as diabetes [16]. As highly conserved, short-non-coding RNAS (21–25 nucleotide in length), mi RNAs negatively regulate gene expression post-transcriptional level by