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Review Article

MicroRNA-15a Regulates BDNF Gene Expression: An Approach Towards Type 2 Diabetic Retinopathy

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Abstract: Type 2 Diabetic Retinopathy (T2DR) is one of the most communal diabetic eye diseases and a prominent cause of blindness. It is characterized by variations in the blood vessels of the retina. Previous studies have reported that T2DR is allied with neurodegeneration and that apoptosis may occur in diabetic retina. Brain-derived neurotrophic factor (BDNF), which is one of the member of neurotrophin family, is very effective in protecting retina from hyperglycemia in vitro. In addition, BDNF stimulate the expression of tropomyosin-receptor kinase B (TrkB) and elevate the phosphorylation levels of TrkB in retina. As per the available literature reviewed it can be hypothesized that by regulating the expression level of miRNA-15a, expression level of BDNF can be regulated which in turn can normalize the TrkB/MAPK pathway and may protect apoptosis of human retina cells, which provides novel acumens into the pathogenesis of T2DR. Therefore, miR-15a could be a diagnostic and prognostic biomarker and therapeutic target for T2DR.
Keywords: Type 2 Diabetic Retinopathy, hyperglycemia, retina, epigenetics, microRNA-15a, neurotrophin.

IINTRODUCTION

MicroRNAs (miRNAs) are basically small non-coding RNAs that lead to gene silencing through cleavage by means of non-perfect annealing to target genes, destabilization and sometimes even inhibition of mRNA translation. MiRNAs are a large family of 20–22-nucleotide noncoding RNAs that are incorporated in numerous cellular processes [1, 2]. Each miRNA has the target of multiple genes and multiple miRNAs may regulate one gene in turn. MiRNAs are encrypted within the genome (from exonic, intronic or intergenic regions) and are initially transcribed as primary transcripts which are several kilo bases in length. Two RNase III enzymes, Drosha in the nucleus and Dicer in the cytoplasm sequentially cleave primary transcripts, to produce 70 nucleotide long precursor miRNAs (pre-miR) and then mature miRNAs, respectively. To form the RNA-induced silencing complex (RISC) which is a core of a multicomponent gene regulatory complex, single-stranded mature miRNAs associate with Argonaute proteins (Ago) [3]. For gene regulation via miRNA, three mechanisms have been described-miRNA-mediated mRNA decay; direct mRNA degradation and translation repression. Recent data have guided that the mechanism of repression is predominately via a decrease in mRNA target stability [4]. On various levels ranging from transcription and processing to target site binding and miRNA stability, miRNA activity and abundance is also regulated [5]. Bioinformatics analysis indicates, multiple target mRNAs can be regulated by miRNAs (i.e. nearly 60 % of all mammalian mRNAs represent miRNA targets) and several miRNAs can target individual mRNAs [6]. miRNAs have been linked with a variety of cellular processes and numerous signal transduction pathways [7, 8].Thus, as a repercussion of the extensive range of processes they are able to influence, miRNA deregulation is a hallmark of number of pathological conditions. Hence a unique opportunity is created by targeting one or a few miRNAs leading to prevention of expression of multiple genes and for the development of RNA-based therapeutics. MiRNAs are also recognized as molecules in activities with remarkable modulatory action, in numerous if not all biologic methods [9]. In the previous studies from several groups, it has been observed that alterations of multiple miRNAs in chronic diabetic patients lead to complications including diabetic retinopathy. The list includes miR200b, miR146a, miR195, mir15a etc. [10-12]. However, in most of the studies, researchers had used a particular

miRNA to target a single mRNA. Type 2 Diabetic Retinopathy (T2DR) is a key factor of blindness worldwide and is also nowadays an important area of study in clinical and basic research. Previous studies also focus on the mechanisms underlying microvascular changes. Interestingly, a rapid increase in a number of studies has reported that the pathogenesis of T2DR correlates with neurodegeneration of the retina [13]. Pathogenesis of T2DR may be attributed to Neuronal and glial tissues, which are sensitive to hyperglycemia. Microvascular damage is also likely related to malfunctions of glial cell metabolism [14]. The miR-15 microRNA precursor family is built up of small non-coding RNA genes that regulate gene expression. The family includes the related miRNA-15a (miR-15a) and miRNA-15b (miR-15b) sequences, as well as miR-195, miR-497, miR-16-1 and miR-16-2. These six extremely conserved miRNAs are clustered on three separate chromosomes [15]. MiR-15a and miR-16 are clustered within 0.5 kilo bases at chromosome position 13q14, in humans [16]. In human diseases, miR-15a family miRNAs have been involved, therefore miR-15a acts as a biomarker for the treatment of T2DR [17]. Thus, important objectives of further studies are understanding the pathological changes that correlate with T2DR and the mechanisms that protect the retina. Studies in animal models have demonstrated that at early stages of T2DR, specific retinal ganglion cells (RGCs) undergo apoptosis and retinal neurodegeneration is likely to occur due to lack of brain-derived neurotrophic factor (BDNF) which is a member of neurotrophin family of growth factors vital for cell survival [18].

II. MiRNA-15a AND TYPE 2 DIABETIC RETINOPATHY

MiR-15a could be a key miRNA within the diabetic retina tissue layer [19]. In eyes of patients with proliferative diabetic retinopathy (PDR), higher levels of hsa-miR-15a were reported [20]. It was also reported that miR-15a was elevated in early endothelial progenitor cells [21]. ARVO 2015 Annual Meeting Abstracts on Diabetic Retinopathy by *Kamalden* et al., have suggested that in patients with T2DR, miRNA-15a is upregulated as the rigorousness of T2DR increases. By targeting Akt3, MiR-15a considerably upsurges oxidative stress as demonstrated by over-expressing miR-15a in patients of T2DR. Under high glucose and hypoxic stress, pancreatic β-cells produce considerably much higher levels of miR-15a. In mouse model findings were validated, where considerably higher miR-15a expression was observed in both blood-derived exosomes and in the retina. This reading not only accentuates the role of miR-15a in the pathogenesis of T2DR, however also advises that miR-15a possibly will aid as a potential candidate for a diagnostic, prognostic, and predictive biomarker for T2DR. According to the past study, this was the first proof demonstrating that as T2D grows, the transcription of miR-15a is stimulated by pancreatic β-cells to meet an augmented insulin demand. This surplus miR-15a move into the blood stream via exosomes, which then transport miR-15a into the retina. This inimitable observation illuminate the rousing potential for miRNAs as diagnostic biomarkers for T2D complications, and luckily may also prove to be a novel target in terms of therapeutics to prevent T2DR [22].

III. BDNF GENE AND PROTEIN STRUCTURE

The BDNF gene (in humans on chromosome 11p) has four 5′ exons (exons I-IV) that are associated with distinct promoters, and one 3′ exon (exon V) that encodes the mature BDNF protein [23, 24]. In a study, eight distinct mRNAs were transcribed, with transcripts containing exons I-III expressed predominantly in brain and exon IV being found in lung and heart [24]. In brain and neuronal cells, in vivo and in vitro studies advice that growth, cell differentiation, synaptic connectivity, plasticity, and cell survival is affected by BDNF [25-28]. High affinity tropomyosin-related kinase B (TrkB) receptor mediates biological function of BDNF [27]. Rohrer et al. revealed that serious variations in retinal function is triggered by the absence of BDNF or its receptor [29]. Moreover, it has been observed that BDNF diminishes injuries of retinal ganglion cells after optic nerve lesion and shield neurons under oxidative stress circumstances in rodents [30, 31].

The functional activity of BDNF works through two different receptor systems, its high-affinity tropomyosin-related kinase B (TrkB) receptor and the low affinity receptor p75 is a communal non-specific receptor for entire neurotrophins [32]. Dimerization of its receptors is modulated by BDNF binding, and numerous signaling pathways are initiated and activated by the intracellular kinase-binding domain [33, 34].

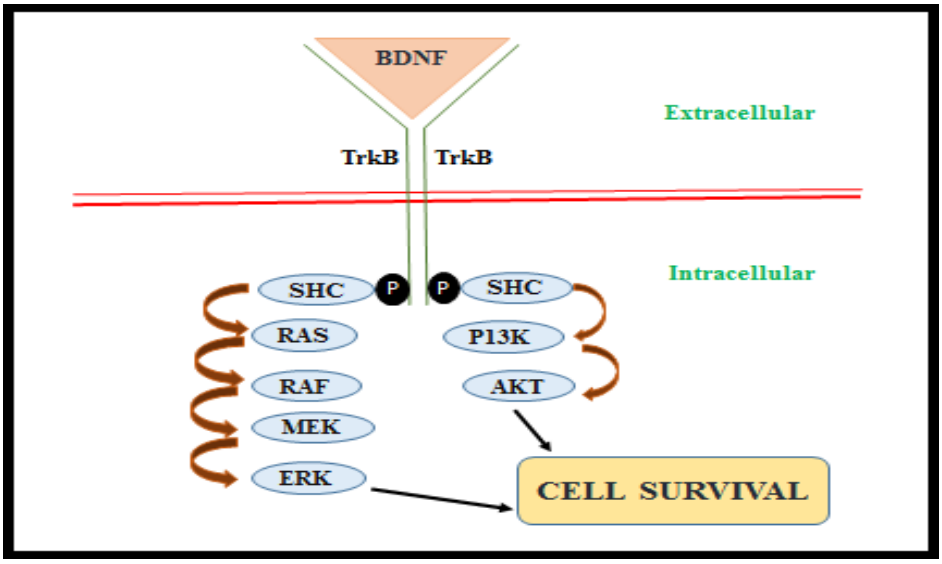

Fig-1: BDNF-TrkB pathway for cell survival [32]

BDNF/TrkB signaling (Ras-Raf-MEK-ERK pathway is also known as MAPK pathway) is vital for growth, differentiation and survival of cells and neurons in retina. To the extracellular domain of TrkB, BDNF binds then formation of homodimers occur to activate downstream intracellular signaling cascades containing several kinases [32].

IV. TYPE 2 DIABETIC RETINOPATHY: AN UPDATE

Type 2 Diabetic retinopathy (T2DR) is one of the complications of diabetes mellitus. Loss of vision occurs due to diabetic maculopathy and complications of proliferative diabetic retinopathy (PDR) such as vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma. By 2030 it is estimated that developing countries will face an increase of 69% and industrialized countries by 20% of the number of patients with diabetes compared to 2010 [35,36].

A number of genetic factors account for 25-50% of the risk of developing T2DR. Therefore, the use of genetic analysis to identify those diabetic patients most prone to developing T2DR might be useful in designing a more individualized treatment. In this context, there are three main research strategies: Genome-Wide Association Studies, linkage studies and candidate gene studies. Genome-Wide Association Studies are a new tool involving a massive estimation of single nucleotide polymorphisms (SNP) in large samples. The linkage studies analyse shared alleles among family members with T2DR under the assumption that these prompt to a more aggressive development of T2DR. Finally, in the candidate gene approach, numerous genes coding proteins closely related to T2DR development have been analyzed [37].

V. PATHOGENESIS OF TYPE 2 DIABETIC RETINOPATHY

Micro-angiopathy due to hyperglycemia in patients with diabetes mellitus results in vascular leakage, which is the prime cause of diabetic macular edema as well as capillary occlusion. Capillary occlusion itself causes retinal ischemia and increased levels of growth factors which leads to the development of neovascularisation and then to the proliferative stage of diabetic retinopathy. More new pathways have been identified which are involved in the pathogenesis of diabetic retinopathy leading to nerve growth factor autophagy, inflammation and epigenetics. Biochemical alterations such as oxidative stress, activation of protein kinase C and the formation of advanced glycation end products have been found as a response of the retina to hyperglycemia [38]. Also, increase in vascular permeability and infiltration of leukocytes and inflammation is attributed to kinin B1 and B2. Especially, kinin B1 is upregulated in the retina of diabetic patients and almost non-existent in normal tissue. These findings find great application in the development of new therapeutic strategies which aim at antagonizing kinin receptors or inhibiting kallikreins [38].

Recent investigations have proved that the whole retinal neurovascular system is impaired by diabetes mellitus which results in loss of neurovascular connection, neuroinflammation and neurodegeneration. This can be detected even before the advent of vascular damage [39]. During the functional examination of diabetic patients, reduced dark adaption, impaired colour and/or contrast vision as well as visual field defects are being observed [40]. During hormonal changes while adolescence and pregnancy, T2DR tends to deteriorate [41].

VI. HYPERGLYCEMIA INCREASE LEVEL OF APOPTOSIS

Apoptosis is regulated by numerous proteins which are associated with canonical mitochondrial or endoplasmic reticulum signaling pathways (anti-apoptotic molecules- Akt, Cox-2). While it is observed that inhibition of cytochrome C release occurs due to diabetes-induced expression of proapoptotic molecules including mitochondrial proteins, AIF, anti-apoptotic proteins- Bcl-2 and Bcl-XL in the outer wall of mitochondria. While Pro-apoptotic Bcl-2 proteins Bad, Bax, Bid and Bim may exist in in the cytosol but they translocate to mitochondria following death signaling, where they induce the release of cytochrome C. Cytochrome C initiates the activation cascade of caspases once released into the cytosol. The generation of superoxide is triggered by the loss of a component of mitochondrial electron transport chain, which leads to apoptosis. This translocation is inhibited by survival factors such as BDNF that induces phosphorylation of Bad leading to its cytosolic sequestration by means of activation of TrkB-ERK pathway, thus, finally preventing apoptosis [42].

VII. BDNF AND TYPE 2 DIABETIC RETINOPATHY

Type 2 Diabetic retinopathy (T2DR), the worldwide cause of blindness, is an important area of study in clinical and molecular research. Previous studies have largely focused on the mechanisms involving microvascular variations. However, an increasing number of studies have reported that the neurodegeneration of the retina is associated with the pathogenesis of T2DR [43]. Retinal tissue which is sensitive in cases pertaining to hyperglycemia, it is said to be involved in the pathogenesis of T2DR. Microvascular damage is also suggested to be associated with malfunctions of endothelial cell metabolism [44]. Studies in animal models have demonstrated that at early stages of T2DR, specific retinal ganglion cells (RGCs) undergo apoptosis whereas lack of brain-derived neurotrophic factor (BDNF) is connected with retinal neurodegeneration [45].

BDNF is a member of the neurotrophin family of growth factors and is critical for the development, differentiation, and maintenance of retina. Previous studies have revealed that BDNF finds great application in photoreceptor cells and the repair of damage in the optic nerve and the retina. BDNF stimulates survival in injured RGCs prompted by axotomy or retinal ischemia, and also supports regeneration of the nerve fibber [46, 47]. In addition, BDNF establishes phenotypes and synaptic connections in the developing retina and also promotes the survival of retinal interneurons [48]. BDNF has been reported to inhibit neuroretinal cell death under conditions of ischemia and hypoxia. It has also found to inhibit apoptosis in rat RGCs at early stages of T2DR [49].

Tropomyosin-receptor kinase B (TrkB) is a receptor protein involved in the development and maturation of the central and peripheral nervous systems. BDNF has a great affinity for TrkB and p75 heightens the interaction between BDNF and TrkB [50]. Upon ligand-binding, TrkB undergoes homodimer-ization, autophosphorylation and activation. It then recruits and stimulates several downstream effectors to regulate gene expression and protect retinal tissue cells. Members of the TrkB downstream signaling cascade such as ERK/MAPK and PI3K/PKB, have been informed to be responsive to BDNF [51]. Several studies have also hypothesized that BDNF largely activates the MAPK pathway [52-55]. A number of *in vivo* studies have demonstrated that the death of retinal neurons at early stages of T2DR connects with the decreased BDNF level, and TrkB is essential for the protection of retinal tissue cells induced by BDNF. However, it was a question of interest whether BDNF will protect retinal tissue cells exposed to hyperglycemia *in vitro* by maintaining the normal level of miR-15a.

The aim was to determine whether by maintaining a normal level of miR-15a, BDNF is effective in protecting retinal cells from hyperglycemia, as BDNF is the target of miR-15a. In addition, by maintaining normal level of miR-15a, which can in turn maintain BDNF, promotes TrkB expression and activates the TrkB/MAPK pathway to decrease level of apoptosis. This review is likely to provide novel visions into the pathogenesis of T2DR and can prove to be useful for the development of novel treatment strategies for this disease [56].

VIII. THERAPEUTIC UTILITY

Reduced expression of BDNF protein in the brain is a characteristic of T2DR patients whereas exogenous or enhanced endogenous BDNF can alleviate neurological symptoms associated with T2DR [57]. Thus methods that can increase BDNF signaling in the brain can possibly be used in the line of treatment of T2DR.

Inappropriately, the therapeutic utility of BDNF is hampered due to its poor efficiency in crossing the blood-brain barrier. Numerous TrkB agonists have been tested in mouse models for this purpose [58, 59]. In contrast, these small molecules are not BDNF itself. Thus their *in vivo* actions may not be the same as BDNF's. On the basis of recent therapies an effective method of increasing BDNF protein levels in the brain has been lacked. Luckily, there are a number of microRNAs known to regulate BDNF and the present finding suggests that the manipulation of small

miRNA levels could be a potential method for increasing BDNF levels in neurological conditions that involve reduced BDNF [60, 61]. MiR-15a, a miRNA upregulated in retina of T2DR patients, is a regulator of BDNF. High levels of miR-15a repress BDNF which in turn undergo apoptosis of retinal neurons. Regulating level of miR-15a using anti-miR can fulfil the purpose [62]. Hence, this review may provide a novel role for miR-15a in protecting retinal cells from apoptosis, new mechanistic insight into the regulation of BDNF in the context of T2DR.

IX. CONCLUSION

BDNF protects retinal tissue following acute high intraocular pressure by affecting the expression and phosphorylation of the TrkB receptor. However, in *in vitro* conditions, only a limited number of studies have proven to be successful in analysing the protective effect of BDNF on retinal tissue exposed to hyperglycemia. It was identified that increase in the expression and phosphorylation of TrkB and protection of neurons in the retina from hyperglycemia was due to BDNF. In accordance with the previous studies, BDNF was seen to protect retinal cells from hyperglycemia.

As the receptor of BDNF, TrkB is critical for its neuroprotective function. Under the conditions of hyperglycemia, BDNF was shown to upregulate the expression of TrkB at the mRNA and protein levels in retinal cells. Hyperglycemia also leads to higher expression levels of TrkB, which is in accordance with the findings of previous studies that mild brain injury differentially alters neurotrophin and neurotrophin receptor levels [63, 64]. The outcomes of the study specified that the higher expression of TrkB induced by hyperglycemia may be a compensatory mechanism for self-protection. As the phosphorylation of TrkB is crucial for its activation, in cells under various treatment conditions phosphorylation of TrkB was analyzed.

Apoptosis is a form of programmed cell death that is important in multicellular organisms. Canonical mitochondrial or endoplasmic reticulum signaling pathways are numerous proteins associated with Apoptosis. Previous studies have reported that normal retinal cells constitutively express the antiapoptotic molecules, Akt, Cox-2 and Mcl-1, while diabetes induces the expression of proapoptotic molecules, together with mitochondrial proteins, AIF and cytochrome C [65]. It was hypothesized that adding extra neurotrophin may protect diabetic neurons as apoptosis in diabetic neurons is associated with the lack of neurotrophic factors. The results confirmed that by decreasing the rate of apoptosis, BDNF protects retinal neurons from hyperglycemia. As a regulator of apoptosis, the Ras-MAPK pathway was previously reported to be downstream of TrkB. BDNF activates the TrkB/MAPK pathway and inhibits apoptosis, thus promoting the survival of retinal cells from hyperglycemia. The results of the findings indicate that TrkB and MAPK are involved in neuroprotection against hyperglycemia induced by BDNF [56].

MiRNA-15a form an important regulatory network by controlling the levels of BDNF in retina. Deciphering such a mechanism represents a step toward unraveling the regulatory network that underlies diabetic complications. This brings us closer to an approach towards personalized medicine for Type 2 Diabetic Retinopathy.

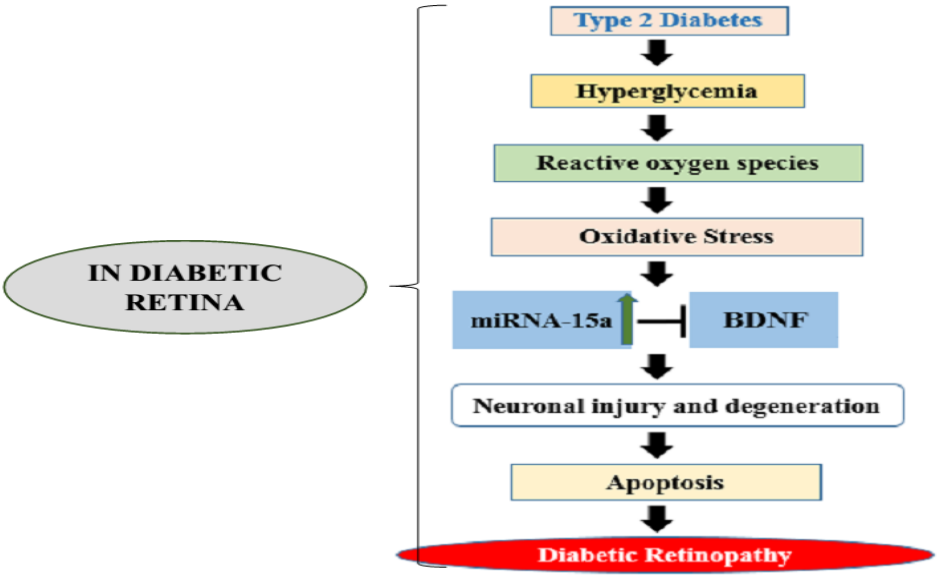

Fig-2: The molecular pathway leading to Diabetic Retinopathy

In retina, neurotrophic factors play a vital role in the expansion and progression of T2DR. Upon oxidative stress signals in the retina due to hyperglycemic conditions, there is overexpression of miRNA-15a which inhibit BDNF due to which the retina neural cells undergo apoptosis with a simultaneous increase in vascular leakage and macular edema leading to vision loss.

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