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MicroRNAs Mediated Regulation of Brain Derived Neurotrophic Factor Expression in Type 2 Diabetes Retinopathy

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Abstract: Type 2 Diabetic Retinopathy (T2DR) is one of the most common impediments of diabetes that affect the blood vessels of the retina, leading to loss of vision. At the advance proliferative stage of diabetic retinopathy, retina triggers the abnormal angiogenesis, which is instigated due to the increased expression of growth factors such as vascular endothelial growth factor (VEGF), Insulin-like growth factor (IGF-1). Existing therapies are solely directed towards advanced T2DR stages often following permanent damage and are therefore highly anticipated for treatments that are preventive or address early pathology. It is suggested that apoptosis is experienced at the early stages of T2DR in specific retinal ganglions and retinal neurodegeneration probably involves an inadequate level of BDNF. Neuroprotection therapeutic strategies, including somatostatin, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are more substantial. BDNF, a Neurotrophic factor derived from brain, also known as ANON2, BULN2 is a neurotrophin, and previous studies have reported decreases in BDNF levels in diabetic retina, causing damage to neurons, resulting in neurodegeneration due to its abuse of retinal neurons through the TrkB / ERK / MAPK pathway. MicroRNA (miRNAs) is a class of small, endogenous transcripts of RNA shaped like hairpin with a length of 21 to 25 nucleotides. As stated in the literature, miRNAs bind their target mRNAs to the 5' end through a completely complementary seed of 7–8 nucleotides and a less complementary area at the 3' end, which leads to translational repression or mRNA degradation. Finally, this review will help us to better understand molecular mechanisms through which miRNAs may be viewed as diagnostic or predictive biomarkers and, most importantly, therapeutic targets.

Keywords: Type 2 Diabetes Retinopathy, BDNF, miRNA-mRNA interactions, Therapeutic agent.

I. INTRODUCTION

Diabetic retinopathy is the most prominent cause of blindness in adults afflicted by more than 90% of patients with 20 years of diabetes. It is accountable for 4.8 percent of the worldwide blindness, correlated with 37 million cases of eye disease. With diabetes frequency increasing at a disturbing proportion, it is estimated that the number of people with diabetic retinopathy will rise from 126.6 million in 2010 to 191.0 million by 2030. ¹ India has emerged as the world's diabetic capital. According to the WHO, diabetes mellitus (DM) affected 31.7 million people in India in 2000. It is estimated that this figure will rise to 79.4 million by 2030, the largest number in any country in the world. Nearly two-thirds of all Type 2 diabetics and nearly all Type 1 diabetics are likely to develop T2DR over time. ² Diabetic retinopathy is intended to result from microvascular changes in the circulation of the retinal system. In the initial stage, there is microvascular occlusion and dilation that has malformed to abnormal angiogenesis resulting in proliferative retinopathy. With the passing stage, the incidence of diabetes increases gradually. ³

A. Progressive Stages Of Diabetes Retinopathy

Recurrent high diabetes blood sugar is associated with damage to the retina's small blood vessels, leading to diabetic retinopathy. The retina detects light and converts it through the optic nerve to signals sent to the brain. Diabetic retinopathy causes fluid hemorrhage of the blood vessels in the retina, which further distorts vision. Abnormal angiogenesis proliferate on the surface of the retina in its most progressive stage, resulting in scarring and cell damage. Diabetic retinopathy advances through two major stages:

- 1) *Non-proliferative Diabetic Retinopathy (NPDR):* Small regions of balloon-like engorgement in the tiny blood vessels of the retina, called microaneurysms that can drip fluid into the retina. Blood vessels that nurture the retina may swell at this stage and be incapable of carrying blood. Several blood vessels are blocked and blood supply to the retina areas is degraded. These areas secrete growth factors that makes retina to grow new blood vessels.

2) *Proliferative Diabetic Retinopathy (PDR)*: Growth factors secreted by the retina in its advanced stage result in the proliferation of new blood vessels that grow along the inner surface of the retina and into the vitreous gel, the fluid that fills the eye. Brittle are the new blood vessels, making them more likely to leak and bleed. The cicatric tissue can contract and cause retinal detachment, resulting in permanent vision loss.⁴

B. Mechanism of Diabetic Retinopathy

A variety of pathophysiological events identified in the progression of diabetic retinopathy are associated with hyperglycaemia and genetic predisposition.⁵ To date, numerous major mechanisms, including the polyol pathway, non-enzymatic glycation, protein kinase C (PKC) activation, are alleged to induce retinal stress in T2DR. All the pathways were involved in microvascular damage and retinopathy development. The pathway of polyol is a two-step metabolic pathway which converts glucose to sorbitol, and then to fructose. In the⁶⁻⁷ initial step, aldose reductase in a NADPH-dependent manner reduces glucose to sorbitol, alcohol. Sorbitol dehydrogenase, which uses NAD⁺ as a cofactor, will metabolize sorbitol to fructose. It causes osmotic damage to retinal vascular endothelium, loss of pericyte, and thickening of basement membrane.⁸⁻⁹ Due to increased activity in the sorbitol pathway, known to generate oxidative stress that contributes to diabetic complications¹⁰⁻¹¹ due to the depletion of antioxidants, primarily glutathione (GSH), ascorbate and Taurine.^{10,12} Sorbitol-generated fructose is a more powerful glycating agent than glucose.¹³ Advanced glycation end products (AGEs) are post-translationally modified proteins and lipids that after exposure to aldose sugar are non-enzymatically glycated and oxidized.¹⁴ AGEs were involved in the loss of vision, more specifically in cataract development, macular degeneration.¹⁵ AGEs affect cellular functions by cross-linking key molecules in the basement membrane or by initiating signalling cascades that alter cell functions (upregulation of NF - kappa B, NADPH oxidase, mitogen activated protein kinases (MAPK), intercellular adhesion molecule-1 (ICAM 1), VEGF, cytokines, and decreased nitric oxide.¹⁶ In T2DR, activation of protein kinase C (PKC) may lead to increased permeability, changes in the flow of retinal blood, and abnormal angiogenesis.¹⁷⁻¹⁹ Furthermore, high glucose activation of PKC encourages the expression of the permeability enhancing factor VEGF in endothelial vascular cells and smooth muscle cells.²⁰⁻²² A numbers of PKC isoforms are expressed in the retina. Many studies have shown an increase in PKC- β -1 and β -2 activity compared to other isoforms, which associates their role in retina complications caused by early diabetes.^{23,24}

In addition, under hyperglycemic conditions, however to a lesser degree than PKC- β -1 and β -2, there was increased activity of PKC- α , γ , and δ . In addition, it is also studied that PKC- ζ based inhibition decreases retinal vascular leakage by attenuating the VEGF and AGE-induced decrease in tight junction proteins, which demonstrates its deep-rooted involvement in T2DR^{25,26} (Figure 1).

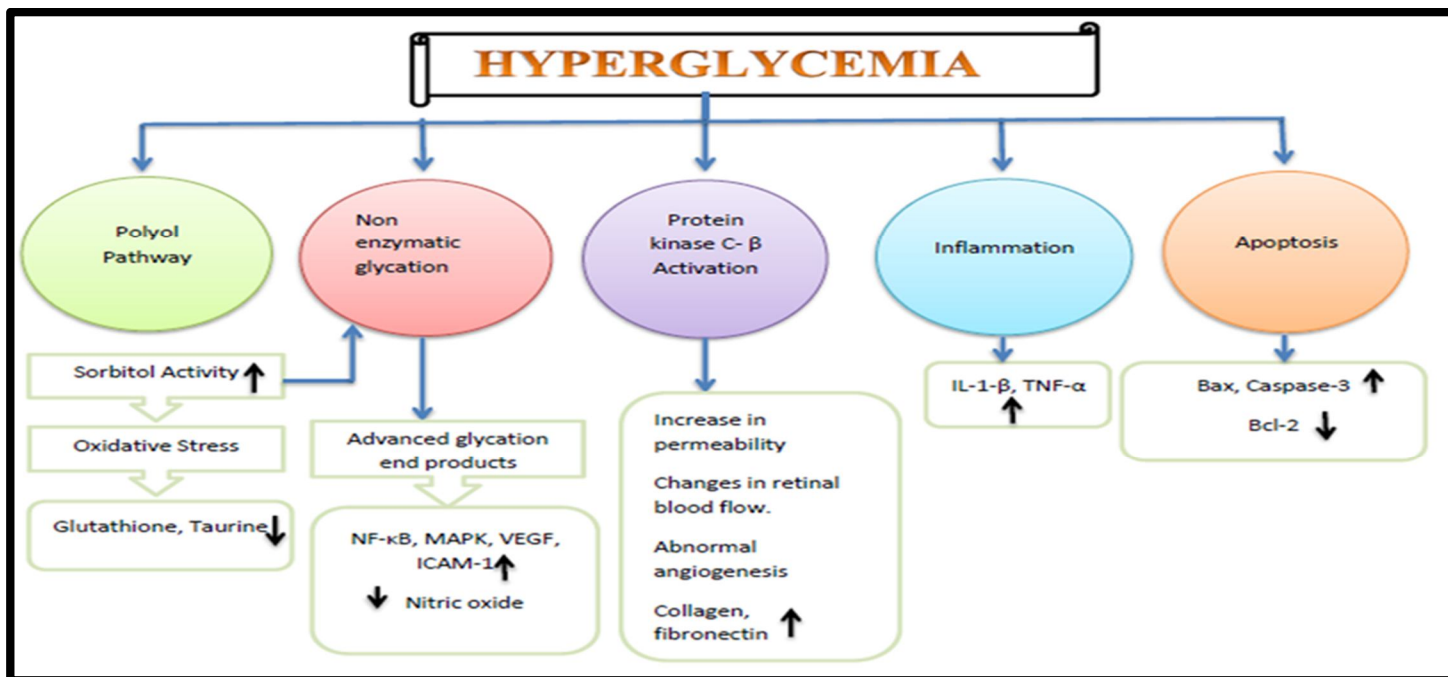


Figure 1: Schematic diagram of the factors responsible for diabetic retinopathy due to hyperglycemic conditions.

II. NEUROTROPHINS AND ITS SIGNIFICANCE

Neurotrophins are a clan of growth factors which are imperative regulators of neural survival, development, synaptic functions, and plasticity. Neurotrophic factors include nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3(NT-3) and neurotrophin-4/5(NT-4/5). Each neurotrophin binds to one of the Trk family of high - affinity tyrosine kinase receptors, with TrkA binding of NGF, TrkB binding of BDNF and NT-4, and TrkC binding of NT-3. Neurotrophins use their survival effects by binding to their TrkB receptor and initiating signalling pathways involving phosphatidylinositol 3 kinase (PI3K)/Akt, leading deactivation of pro-apoptotic targets, and extracellular signal-regulated kinase (ERK), resulting in phosphorylation of the (CREB) cAMP response element binding protein. The transcription of several genes associated with neuronal survival is further encouraged. They can also bind to the p75 (p75NTR) low-affinity neurotrophin receptor and induce programmed cell death, and these neurotrophin contrasting effects are important for regulating the development of neurons, including retinal ganglion cells (RGCs). TrkA is expressed in the RGCs in the retina and p75NTR is expressed predominantly in the Muller glia. Stimulation of these receptors in neurons may produce contrasting effects in which activation of TrkA is accompanied by neuronal survival while activation of p75NTR is associated with neuronal apoptosis.

They also regulate cell fate decisions, axon growth, dendrite growth, and protein expression such as ion channels, biosynthetic enzymes transmitters, and neuropeptide transmitters vital to normal neuronal function²⁷⁻²⁹ (Figure 2).

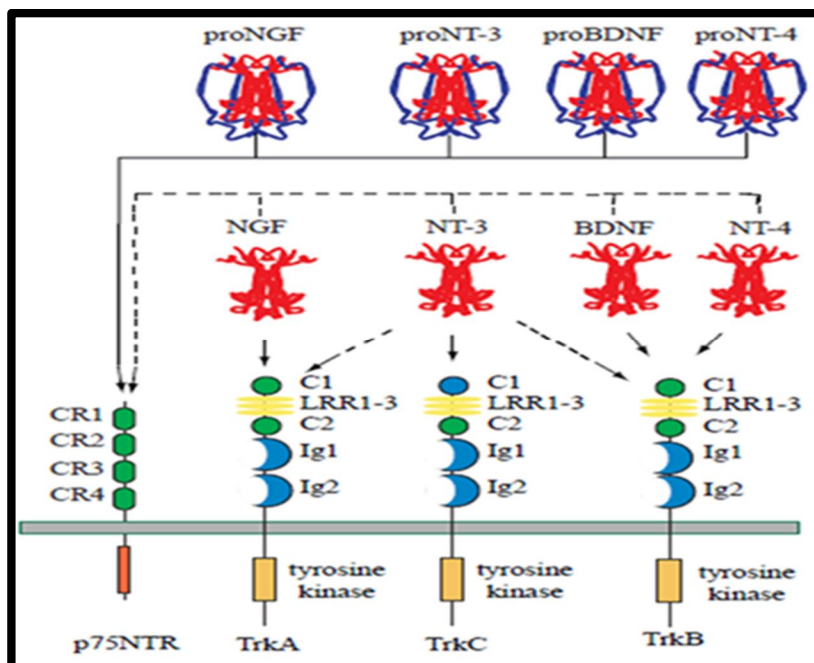


Figure 2: Illustration of Four major Neurotrophin-Receptor interactions. Each proneurotrophin binds with P75NTR but NGF, NT-4, BDNF and NT-3 binds specifically to TrkA, TrkB and TrkC respectively.²⁷

III. ROLE OF BDNF IN TYPE 2 DIABETIC RETINOPATHY

Dysregulation of neurotrophic factors in diseases, such as diabetic retinopathy itself, has been found to be the most prominent cause of neurodegeneration and pathological angiogenesis. BDNF is one of the most important neurotrophins whose level in diabetic retinopathy is gradually transformed. It changes the level of many trophic factors/signals in the retina, reduces the strong signals of survival and increases apoptosis. Neurons and glial cells are known to support neuronal cells, which produce BDNF. BDNF has a greater effect on cell differentiation, synaptic connectivity, plasticity, grow-up, and cell survival, both in vivo and in vitro study in the brain and neuronal cells.³⁰⁻³² It is known that with the help of the high-affinity tyrosine kinase receptors, the biological function of BDNF is facilitated.

The effect of BDNF is primarily dependent on the level and linkage of the receptor and the downstream signal follows after the activation of the receptor.³³ Rohrer et al. showed that the lack of BDNF or its receptor caused serious alterations in retinal function.^{34,35} BDNF has also been shown to decrease retinal ganglion cell damage following optic nerve injuries and to protect neurons in rodents from oxidative stress.

Furthermore, BDNF also protects the retina against ischemic injuries, encourages interneuron survival and plays an indispensable role in the synaptic connections of many neurons.³⁶⁻⁴⁰ Many studies in diabetic patients, as well as diabetic animal serum, have shown decreased BDNF levels. The reduced degree of BDNF, the decrease in glucose and lipid metabolism and the increase in food consumption, are also mainly associated with insulin resistance.⁴¹⁻⁴²

Within the animal diabetes model, few trials have shown that decreased BDNF levels in diabetic retina can lead to neural damage.⁴³⁻⁴⁵ At various stages, BDNF as a prime neurotrophin has been suspected of having a critical role in T2DR as shown in Figure. 3. The part played by BDNF is still not fully stated, nevertheless. The regulation of the BDNF levels in diabetic retina is therefore expected to be a favourable therapeutic target for neuron protection.

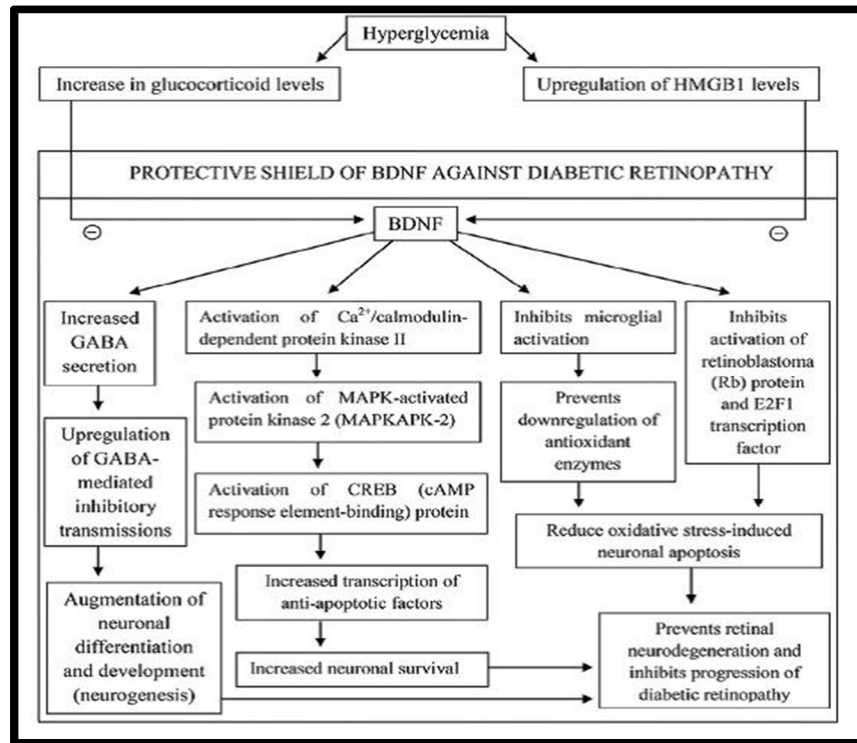


Figure 3: Hyperglycemia-induced down-regulation of defensive effects of brain-derived neurotrophic factor against oxidative stress-induced retinal neurodegeneration and advancement of diabetic retinopathy.⁵⁶

IV. MICRORNAS: A POTENTIAL THERAPEUTIC AGENT

miRNAs are a group of short (approximately 21 to 23 nucleotides long) and highly conserved endogenous non-coding RNAs that modulate gene expression in the 3' untranslated zone (3'-UTR) of various target genes by providing a binding effect on transcript and post-transcription regulation, induced mRNA degradation or inhibiting protein translation. In animals, miRNAs are synthesized by the action of two RNase III-type proteins, the drosha in nucleus, and dicer in cytoplasm, in two stages from the primary miRNAs (pri-miRNAs). In plants, pri-miRNA is completely processed into a mature miRNA in the nucleus by a single RNase III enzyme (DCL1) (Dicer-like 1). The mature miRNAs are then linked to the subfamily proteins Argonaute (Ago). These miRNAs target mRNAs and function thereby as post-transcriptional regulators.⁴⁶

The ultimate biological impact on cells is obvious by repressing specific proteins that are involved in a specific biological pathway. Instead, more than 60% of mRNAs have predicted that multiple miRNAs will be binding at sites which allow for simultaneous interaction with multifaceted miRNAs.⁴⁷ The use of a single miRNA is possible. It is expressed in all types of human cells and it is a crucial part of key organic processes like cell growth, differentiation and apoptosis.

The function and biogenesis of miRNA is therefore expected to be regulated as they have a decisive role in wide range of human conditions, including Alzheimer's (AD) disease, Huntington's, Major Depressive Disorders (MDD), Type 2 Diabetic Retinopathy and an extensive range of cancer developments associated with these conditions. miRNA-21 targets tumor suppressor genes and upregulation and it is also found to be involved in variety of cancers including breast, ovary, cervical, colon, lung, liver, brain, esophagus, prostate, pancreatic and thyroid disease⁴⁸ (Figure 4).

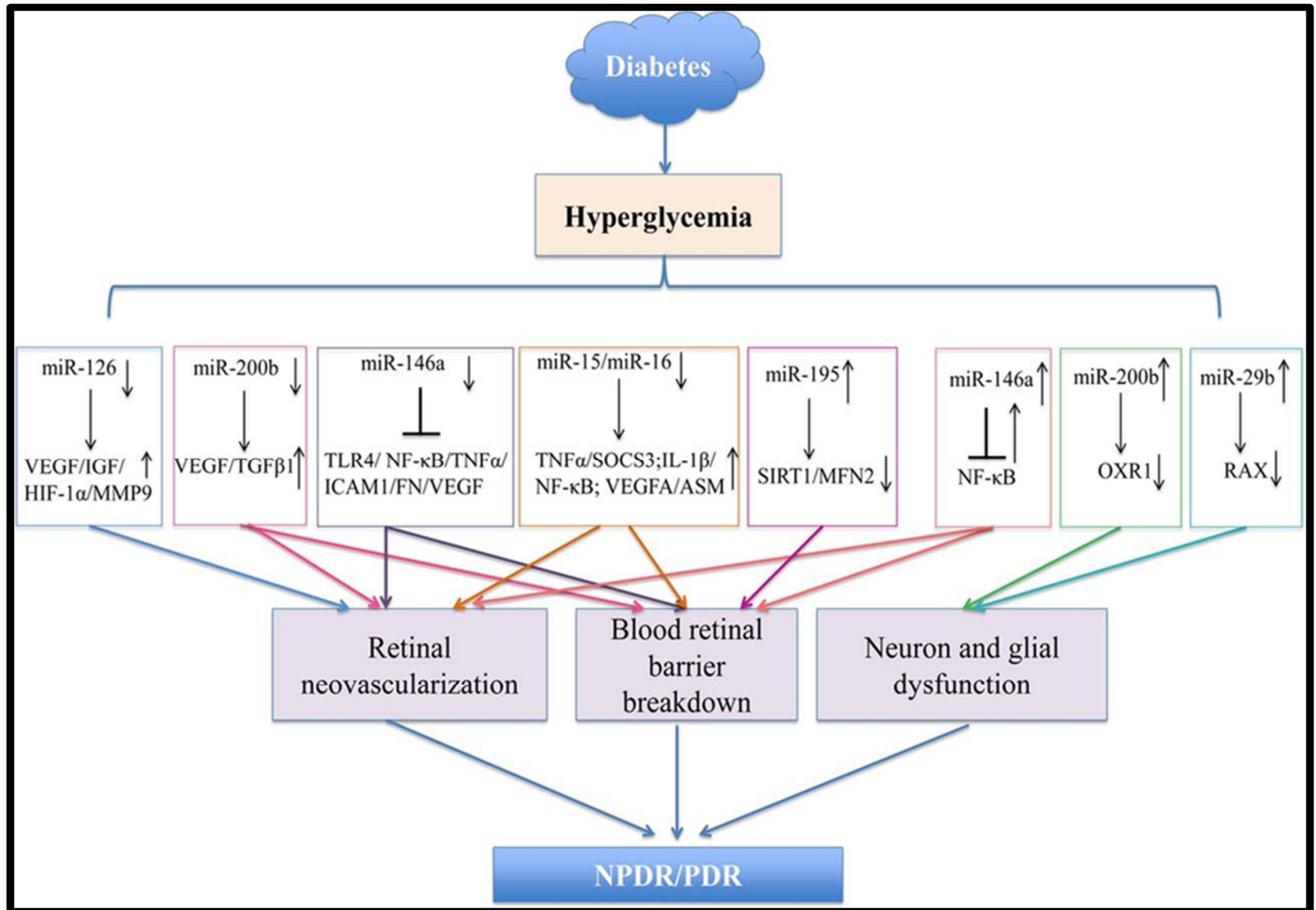


Figure 4: Major microRNA mediated interactions with target genes involved in the progression of T2DR,⁵⁵

V. MICRORNA MEDIATED REGULATION OF BDNF

In a study proposed by Tiao-lai et al., 2017 patients with MDD and healthy controls were enrolled and their serum BDNF protein, BDNF mRNA, and ten miRNAs related to BDNF (miR-16, miR-30e, miR-34c-5p, miR-128, miR-132, miR-134, miR-182, miR-183, miR-185, miR-212) levels were measured and analyzed. By means of independent t-test analysis it was found that serum miR-30e, miR-132, miR-185, and miR-212 levels were greater than in patients with MDD at baseline equated to healthy controls, and BDNF protein and mRNA levels increased expressively after antidepressant treatment, signifying miRNA could be used as a prospective diagnostic biomarker.⁴⁹

In an Alzheimer's disease transgenic mouse model, miR-206 decreased the BDNF levels in cellular extracted and secreted BDNF and indicated that miR-206 is the negative regulator of BDNF. The cellular and secreted BDNF were found to be increased in the presence of inhibitor of miR-206.⁵⁰

A number of studies have also proposed the association of miR-146a with inflammation in T2DR. Extracellular adenosine, which activates adenosine receptors, can encourage anti-inflammatory processes. It has been found that miR-146b discusses changes for macrophages treated by AGA, substantially enhances HREC permeability, rescues disturbed ZO-1(zonula occludens) patterns and increased leukocyte adhesion to ICAM-1. This can be a valuable tool for preserving the blood-retinal barrier function in the T2DR by inhibiting adenosine deaminase ADA2 through miR-146b-3p.⁵¹

miR-200b, the miRNA that has been most studied since first discovered. Expression of miR-200b is reduced after one month following the onset of diabetes in endothelial cells treated with high glucose and in rats with STZ-induced diabetic rats, whereas it's direct validated target, VEGF, is enhanced both at mRNA level and at protein level.⁵² Overexpression of miR-200b improves the expression of VEGF to diabetic rat retinas and prevents increment of glucose-induced permeability and angiogenesis. In contrast, a miR-200b adversary can escalate production of VEGF and further demonstrate its role in T2DR pathogenesis.⁵³ It is also found

that all the miRNAs given below miR-1, miR-10b, miR-155 and miR-191 are directly targeting BDNF by binding to their predicted locations in BDNF 3'UTR using silico approaches, reporters systems, and analysis of endogenous BDNF. It was experimentally deduced that the overexpression of miR-1 and miR-10b leads to suppression of endogenous levels of the BDNF protein whereas; the increase in the level of BDNF mRNA and protein was shown when miR-10b is silenced.

In inference with the data from two cell lines including Human primary glioblastoma U-87 MG cells and Human retinal pigment epithelium 19 ARPE-19, exposed that endogenous miR-1/206 and miR-10 family miRNAs act supportively in subduing BDNF through their predicted sites in BDNF 3'UTR. Finally, miR-1 miR-10b, miR-155 and miR-191, as new regulators, could be used as a possible therapeutic target for BDNF's long and short 3'UTR isoforms. Analysing the complete interactions of BDNF 3'UTR with miR-1, a further family members in the miR-1/206 family, also confirms the interpretation of miR-1 data through *in silico*, that miR-1, and miR-206 share binding sites in BDNF 3'UTR. However, miR-1 and miR-206 differ from the seed sequence with four nucleotides. In this way the miR-206 and BDNF 3'UTR interaction in the whole length of 3'UTR would be quite motivating to analyze. Western blotting revealed that miR-206 decreased BDNF level and decreased the level of both BDNF in cellular extract and secreted BDNF, while it has been shown in a study of a transgenic mouse pattern of Alzheimer's disease that there was an increment of cellular and secreted BDNF because of the miR-206 inhibitor. It is important to suggest that miR-206 inhibition results in an increased brain BDNF level as well as memory performance in AD mice from the therapeutic point of view^{51,54} (Figure 5).

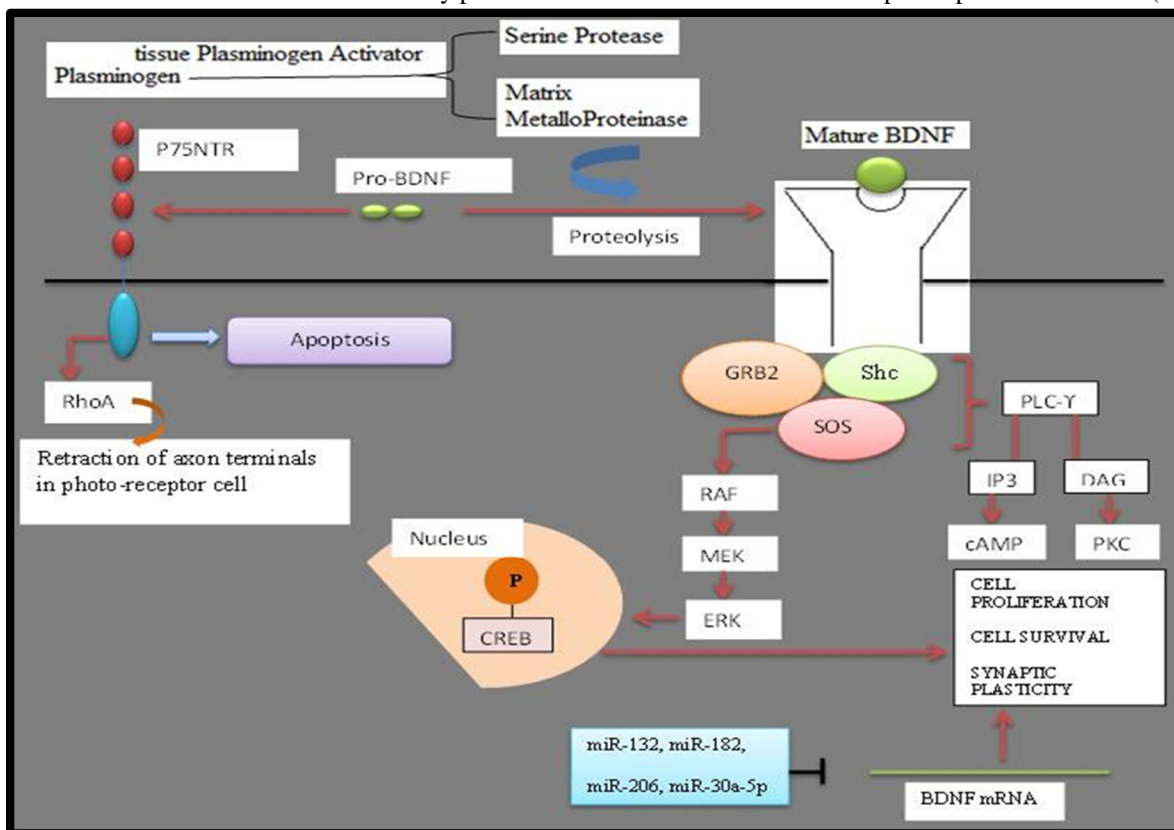


Figure 5: Schematic representation of the various interaction involved in the regulation of brain-derived neurotrophic factor (BDNF) and miR-206, miR-132, miR-182, miR-30a-5p via TrkB/MAPK signaling pathway. Adapted from: <https://link.springer.com/article/10.1007/s12017-016-8407-9>

VI. CONCLUSIONS

In this Review, there are numerous studies showing the role of miRNAs as a regulator of BDNF. In context of disease models such as Alzheimer's disease, Major depressive disorder and Type 2 Diabetic Retinopathy where miRNA continues to play a pivotal role in regulating gene expression directly or indirectly to the prevention of particular ailment. The miRNAs could possibly control the BDNF expression level to help in the therapeutic treatment of Type 2 Diabetic Retinopathy. It could also be suggested that regulation of miRNA could maintain BDNF mRNA expression level which will further prevent retinal neurodegeneration and inhibit the progression of T2DR. It may also provide knowledge for diagnosis of the disease for personalized medicine.

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