

BDNF Gene Mediated Alteration in Type 2 Diabetic Retinopathy a Conceptual Approach to Study MicroRNA- 10b modification via Epigenetic Approach

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ABSTRACT:Type 2 Diabetic Retinopathy (T2DR) is one of the common complications of diabetes and a prominent cause of blindness. It is characterized by variations in the blood vessels of the retina. According to the previous studies T2DR is allied with neurodegeneration and that apoptosis may occur in diabetic retina. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family. As per the available literature the overexpression of miR-10b suppresses endogenous BDNF protein levels and that silencing endogenous miR-10b increase BDNF mRNA and protein levels. Hence the idea of this review article is to check the level miR-10b in terms of T2DR, through epigenetic modification. miR-10b, as novel regulators of BDNF long and short 3'UTR isoforms, supporting future research in different physiological and pathological contexts. Finding the relationship between BDNF and Type II Diabetic Retinopathy giving a way to understand the mechanism of disease and also giving knowledge for diagnosis of the disease for personalized medicine.

KEYWORDS: Epigenetics, BDNF (Brain-derived neurotrophic factor), microRNA-10b, Type II Diabetic Retinopathy.

I. INTRODUCTION

Type 2 Diabetic Retinopathy, a disease of the retina, is the leading reason of acquired blindness in working adults. The microvasculature of the retina is injured, the blood vessels swell and leak fluid, and if not prevented, new vessels start to grow, and ultimately lead to the detachment of the retina (1, 2). Type 2 Diabetic Retinopathy remains the leading reason of blindness in young adults affecting over 90% patients with 20 years of diabetes. The disease carries a heavy burden on our society as it is responsible for 4.8% of the 37 million cases of eye disease related blindness worldwide. With the incidence of diabetes increasing at an alarming rate, the number of people with diabetic retinopathy is expected to grow from 126.6 million in 2010 to 191.0 million by 2030 (3). Increased vascular endothelial growth factor (VEGF), promoting angiogenesis and increased permeability, is a key mechanistic abnormality in Type 2 Diabetic Retinopathy. It is a duration-dependent disease that develops in stages; the occurrence of retinopathy is rarely detected in the first few years of diabetes, but the occurrence increases to 50% by 10 years, and to 90% by 25 years of diabetes. The prevalence of diabetic retinopathy is increasing due to prolonged survival of diabetic patients (4). Chronic hyperglycemia results in oxidative stress and capillary injury in the retina. In an effort to compensate for the loss, a cascade of events is initiated to form new blood vessels. The thus formed vessels are fragile and leaky, causing edema

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all over the retina resulting in visual impairment aided by other features such as basement membrane thickening, blood-retina barrier breakdown, loss of pericytes, etc.(5).

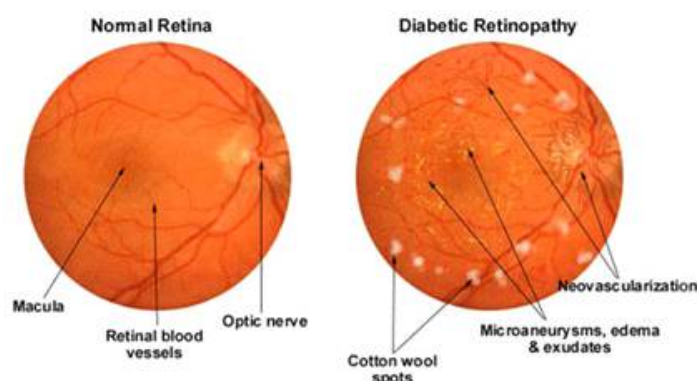


Fig 1:- Normal retina and Type 2 Diabetic Retinopathy affected retina.

(<https://www.murdocheye.com.au/diabetic-retinopathy/>)

II. GENETICS AND DIABETIC RETINOPATHY

Pathogenesis of any type of disease is also influenced by genetic factors, and due to variability in the severity of retinopathy among diabetic patients with similar risk factors, the role of genetic factors in diabetic retinopathy should be somewhat predictable. However, such genetic associations are not yet clearly established. Landmark “Genome-Wide Association Studies” have identified number of genetic variants that could explain some of the inter individual variations in the susceptibility of diabetes (6). A meta- analysis study is a type of study which used to investigate possible genetic associations with Type 2 Diabetic Retinopathy, which incorporated reports published between January 1990 and August 2008, has exposed a significant dissimilarity in the AKR1B1 gene. This gene encodes aldo-ketoreductase family 1 member B1, which is the rate limiting enzyme of the polyol pathway one of the pathways implicated in the development of diabetic retinopathy (1, 7-8). Another meta-analysis study has shown that Ala allele of the Pro12Ala polymorphism in the peroxisome proliferator-activated receptor- γ 2 gene acts as a protective gene in the incidence of retinopathy in type 2 diabetic patients (9). In contrast, recent studies have failed to find any associations between VEGF-related SNPs (rs6921438 and rs10738760) and the risk of Diabetic Retinopathy and nephropathy in diabetic patients (10). Thus, the association between genetic factors and diabetic retinopathy remains to be clarified. The prospect of rising diabetic retinopathy is connected to the duration of the disease. Type 2 diabetes has a dangerous beginning and can go unobserved for years. As a result, patients may already have Type 2 Diabetic Retinopathy at the time of diagnosis. Type I diabetics, on the other hand, are diagnosed early in the course of their disease, and they typically do not develop retinopathy until years after the diagnosis is made. The risk of rising retinopathy increases after puberty. Twenty years after the diagnosis of diabetes, 80% of Type 2 Diabetics and nearly all type I diabetics show some signs of retinopathy(11).

III. ANATOMY OF RETINA

The retina is a type of multi-layered sheet composed of neurons, photoreceptors, and support cells. It is one of the most important metabolically active organs in the body, and as a result, it is extremely sensitive to ischemia and nutrient imbalances (1). The outer one-third part of the retina receives its blood supply from the choriocapillaris, a vascular network that lies between the retina and sclera. The inner two-thirds part of the retina is supplied by branches of the central retinal artery, which comes from the ophthalmic artery (the first branch off of the internal carotid artery). The central retinal artery exits out of the optic nerve and its branches arch temporally both above and below the macula (the sensitive region of the retina responsible for central vision). Although the pathophysiology of diabetic microvascular

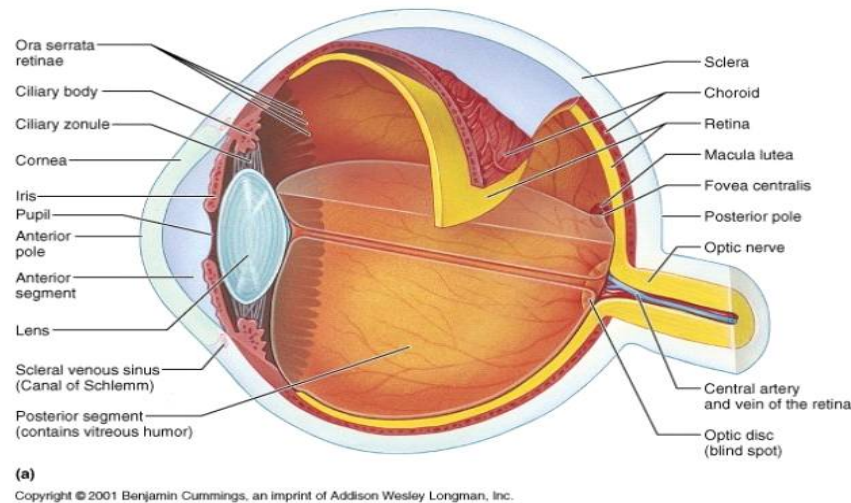
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disease is nebulous, and endothelial cells is damaged through hyperglycemia, selective loss of pericytes, and basement membrane thickening, all of which contribute to leaky, incompetent blood vessels (12).



(a)
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Fig 2:- Anatomy of retina

(<http://www.slideshare.net/FUTUREDESIGNER/anatomy-of-the-retina>)

Type 2 Diabetic Retinopathy is a serious sight-threatening disease and the leading cause of blindness among people with diabetes. Type 2 Diabetic Retinopathy is widely recognized as a neuro-vascular disease as opposed to being previously considered solely as a vascular disease. Numerous retinal functional tests early in Type 2 Diabetic Retinopathy patients and a number of cellular and molecular studies in the retina of experimental diabetic animals suggest that neurons are vulnerable to be damaged shortly after the onset of diabetes before any sign of vascular damage (13-16). A number of studies reported that diabetes causes chronic loss of retinal neurons by increasing the frequency of apoptosis and activation of glial cells (13,-14, 17-18). In the retina, glial and neuronal cells closely interact with retinal vasculature to maintain homeostasis necessary for normal functioning of the retina. Diabetes disturbs the interaction between these cells; however, the precise molecular mechanism of their interaction and dysfunction is not known. Neuronal guidance molecules such as neurotrophic factors play an essential role in the interactions between neuronal and vascular cells, and thereby regulate survival, growth, and functional maintenance of these cells (19-22). Dysregulation of neurotrophic factors has been found to cause neurodegeneration as well as pathologic angiogenesis in diseases such as oxygen-induced retinopathy and proliferative diabetic retinopathy (PDR) (21, 23, 24). Retina, being a neuronal tissue, produces neurotrophic factors such as nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT-4 (25-28). BDNF is produced by neurons and glial cells in the retina which is known for maintenance of neuronal cells (29-31). In vivo and in vitro studies in brain and neuronal cells suggest that BDNF affects cell differentiation, synaptic connectivity, plasticity, growth, and cell survival (29,22, 32, 33). The biological function of BDNF is mediated through high affinity tropomyosin-related kinase B (TrkB) receptor (32, 34), showed that absence of BDNF or its receptor caused serious alterations in retinal function. Furthermore, retinal ganglion cells are damaged by BDNF after optic nerve lesion and protect neurons under oxidative stress conditions in rodents (35, 36). More recently, increasing glutamate uptake and upregulation of glutamine synthetase in Muller cells under hypoxic conditions, Dai and coworkers suggested a neuroprotective effect of BDNF by (37). Numerous studies reported decreased levels of BDNF in the serum of diabetic patients and in diabetic animals, which correlated with insulin resistance, reduced glucose and lipid metabolism, and increased food consumption (38- 40). However, the role of BDNF in Type 2 Diabetic Retinopathy is not fully understood. Little is known about the serum level of BDNF in Type II Diabetic Retinopathy patients and in the serum and retina of diabetic.

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IV. MicroRNA

microRNAs (miRNAs) are a class of highly conserved 19- to 25-nucleotide noncoding RNAs that regulate gene expression at the posttranscriptional level (41). MicroRNAs (miRNAs) are a family of small noncoding single-strand RNA (22 nucleotide) molecules that were first discovered in the nematode *Caenorhabditis elegans* in 1993 (42-43). Transcription of miRNAs occurs through RNA polymerase II (44) and subsequent processing is intermediated by the nuclear ribonuclease III (RNase III) enzyme Droscha to form precursor miRNAs (70–100 nucleotides). microRNAs modulate both physiological and pathological pathways by post-transcriptionally inhibiting the expression of a plethora of target genes (45). Most miRNAs negatively regulate gene expression at the posttranscriptional level, by interacting with their target mRNA 3' untranslated region (UTR). One miRNA may regulate a large number of target genes, and a single gene may also be regulated by multiple miRNAs, targeting various sites of the gene (46). They have been implicated as players in multiple biologic processes such as differentiation, proliferation, apoptosis, and in providing feedback loops for various signal transduction pathways (47, 46). miRNAs also deal with insulin signaling in target tissues, including skeletal, liver and adipose tissues. Insulin resistance describes the failure of target tissues to react adequately to circulating insulin. Insulin resistance in skeletal muscle and adipose tissue decrease glucose uptake and the local storage of triglycerides and glycogen. In case of liver cell insulin resistance leads to reduced glycogen synthesis and storage and concomitant failure to suppress glucose production. The end results are preeminent blood glucose and free fatty acid levels, along with raised insulin levels—hallmarks of the metabolic syndrome. If there is no adequate compensatory increase in pancreatic β -cell function to counteract the insulin resistance, then Type 2 Diabetic Retinopathy results (48). miRNAs can regulate gene expression via different ways, including translational repression; mRNA cleavage, and deadenylation, miRNAs have rapidly emerged as promising targets for the development of novel therapeutics. Double-stranded miRNAs mimics and anti mRNA antisense oligodeoxyribonucleotide are the two commonly investigated techniques to target specific miRNAs. miRNAs have a specific and defined target in the pathogenic mechanism of the disease, miRNAs-based therapy comes with the advantage that they target multiple genes involved in the same pathway process (49).

V. BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF)

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic factor family and is known to protect against neurotoxicity of the $A\beta$ peptide and neural cell death by aggregation of $A\beta$ and tau proteins (50-51). Brain-derived neurotrophic factor (BDNF) is essential in modulating memory-associated neuroplasticity through regulating cell survival, proliferation, and synaptic growth in the developing central nervous system (51-52). BDNF can induce long-term potentiation (LTP), which is considered to be the neurophysiological basis for learning and memory (53). Furthermore, inhibition of BDNF signaling by gene knockout or antisense RNA damages spatial learning and memory (54). Recently, many studies have demonstrated that BDNF serum levels are significantly lowered in patients with cognitive decline associated diseases, such as Huntington's disease (55), Alzheimer's disease (56) and mild cognitive impairment (57).

VI. RELATIONSHIP BETWEEN BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) AND TYPE II DIABETIC RETINOPATHY

Three studies have shown alterations in BDNF levels in the blood of Type 2 Diabetic Retinopathy patients. Two of them reported decreased circulating BDNF levels in Type 2 Diabetic Retinopathy patients (58-59), while another study reported increased serum BDNF levels in newly diagnosed patients with Type 2 Diabetic Retinopathy (60). Although BDNF is mainly focused in the nervous system, it is also found in serum and platelets (61-62). BDNF can cross the blood-brain barrier (61), and BDNF levels in serum have been positively correlated with that of the brain. Accordingly, if circulating BDNF levels reflect BDNF expression in the brain; this could influence cognitive performance in Type 2 Diabetic Retinopathy patients. In the light of cognitive impairment and the significant changes in circulating BDNF that occur in Type 2 Diabetic Retinopathy, and the important role of BDNF in cognition, hence hypothesized that

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altered circulating BDNF may be related with cognitive impairments in Type 2 Diabetic Retinopathy. To our best knowledge, none has examined this association in patients with Type 2 Diabetic Retinopathy.

VII. MICRORNAS -10B

The miR-10 microRNA precursor family encodes a group of short non-coding RNAs which is involved in gene regulation. The miR-10 family is highly conserved and has sparked the interest of many research groups because of the genomic localization in the vicinity of, coexpression with and regulation of the *Hox* gene developmental regulators. Here, the current knowledge of the evolution was reviewed, physiological function and involvement in cancer of this family of microRNAs (63). The mammalian miR-10 family consists of miR-10a and miR-10b, which are encoded upstream of *HOXB4* and *HOXD4*. MiR-10a and miR-10b have identical seed sequences and vary by only a single nucleotide in the mature sequence and they are predicted to share common targets.

miR-10 has gained significant interest because of its co-evolution with, and location within, the *Hox* clusters of developmental regulators (64). *Hox* genes are highly conserved transcription factors that are crucial for correct anterior-posterior patterning of bilaterian animals. As members of the miR-10 family are located in close proximity to *Hox4* paralogs, this family of miRNAs was initially suggested to play a role in the determination of body plans.

VIII. microRNAS AND BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF)

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and has important functions in brain development, synaptogenesis, and memory and learning (65-69). The 3' untranslated regions (3'UTRs) of mammalian genes contain highly conserved sequences (70) important in the regulation of translational efficiency, polyadenylation, and stability of the mRNA. These functions are mediated by binding to RNA-interacting factors, such as microRNAs (miRs) (71-72). One way to modulate miR-mediated regulation of gene expression is through the generation of alternative mRNA transcripts that differ in the length of the 3'UTR (73). Brain-derived neurotrophic factor transcripts contain either short (BDNF-SH, 350 nt) or long 3'UTR (BDNF-L, 2891 nt) (74). In addition to length, secondary structure of the 3'UTR is also known to influence mRNA stability, at least in part by modifying accessibility to miR target sites in the mRNA (75-76). In general, miRNA sites near the ends of the 3'UTR are more effective than sites in the center of the 3'UTR, partly because regions in the middle of the 3'UTR are more likely to be incorporated into hairpin structures, hindering access to miRNA's. BDNF-L contains a stem-loop structure necessary for the regulation of transcript stability (80) raising the possibility that a secondary structure could determine access to factors like miRs that influence mRNA stability. miRNAs have been reported to be involved in the development and function of eyes (81). Retina specific deletion of Dicer, which is essential for miRNA maturation, induces retinal degeneration (80-82). Recent studies have also indicated that miRNAs play important roles in many retinal diseases (83), including retinal neovascularization (84).

IX. CONCLUSION

In this study the role of miRNAs as post transcriptional inhibitor of BDNF and the effect of 3'UTR sequence variation on miRNAs binding capacity was explored. Using in silico approach, identified a group of miRNAs putatively regulating BDNF expression and binding to BDNF 3'UTR polymorphic sequence. And also investigate down regulated expression in miRNAs -10b.

X. SIGNIFICANCE

microRNAs-10b control the BDNF level to help in the therapy of Type 2 Diabetic Retinopathy as miRNA10b a regulator of BDNF gene. Also find the relation between BDNF and Type 2 Diabetic Retinopathy will give a way to understand mechanism of the disease. It may also provide knowledge for diagnosis of the disease for the personalized medicine.

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