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Targeting MicroRNA-15a involved in the BDNF Signaling Impairment in Type 2 Diabetic Retinopathy: A Review

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Abstract: ***In working adolescents all over the world, type 2 diabetic retinopathy (T2DR) is a constantly increasing issue. T2DR was regarded a retinal microvascular condition. However, there is growing proof that the pathogenesis of T2DR is an early occurence of retinal neurodegeneration. Neurotrophic factors play an important role for neuronal development and survival, among the many neurotrophins (NTs) vital for neuronal growth and survival. A strong neuroprotective agent particularly for retinal cells is the brain-derived neurotrophic factor (BDNF). BDNF is attached to its high-affinity tyrosine kinase B (TrkB) receptor and increases its concentrations of phosphorylation in the retina. Previously, low BDNF concentrations were correlated with T2DR pathogenesis. A new class of tiny RNAs, which are non-coded, regulate gene expression after transcription by encouraging degradation or translational repression of target messenger RNA (mRNA), are microRNAs (miRNAs). They are involved in a big number of physiological and pathophysiological procedures, including retinopathy for diabetes. According to the literature studied, enhanced BDNF activity in retinal cells can be assumed to be efficient in defending retinal tissues against harm through the regulation of speech of the microRNA-15a (miR-15a), in turn normalizing the TrkB / MAPK mechanism and preventing the apoptosis of human retina cells, which gives new acuity into T2DR pathogenesis. miR-15a could therefore be regarded to be a appropriate diagnostic, prognostic and therapeutic biomarker for T2DR.***

Keywords: Brain-Derived Neurotrophic growth factor, MicroRNA-15a, Neurodegeneration, Therapeutics, Type 2 Diabetic Retinopathy.

I. INTRODUCTION

The main cause of vision deficiency and preventable blindness is Type 2 diabetic retinopathy (T2DR) [1]. Edema influencing the core or macular retinum (DME macular diabetic edema)[2] causes visual impairment. T2DR has traditionally been regarded as a retinal microvascular disease. However, more proof reveals that premature microvascular shift of the T2DR triggers retinal neurodegeneration [3]. The changes that have been described include the breakdown of the blood-retinal barrier (BRB), vasoregression and impairment of neurovascular interaction [4]. Glia and neurons closely interact with retinal vasculature to maintain the normal function of the retina. Diabetes disturbs the interaction between these cells by damaging neurons due to apoptosis and activating glial cells which is another feature of retinal neurodegeneration [5] Loss of neural cells leads to a decrease in the density of the nerve fiber layer, which has been identified in rats with streptozotocin (STZ) and on the basis of laser scanning or optical coherence tomography for clinical trials. [6-8]. Several experimental models of diabetic retinopathy, have shown that the major triggers of apoptosis that lead to cellular damage include oxidative stressors such as (ROS) [9-12]. An growing amount of information indicates that neuronal guide molecules, such as neurotrophic factors, play a significant role in neuronal-vascular relationships to regulate their survival, development and functional preservation.[13]. Neuronal retina produces a substantial amount of neurotrophic factors such as brain derived neurotrophic factor (BDNF) which affects cell differentiation, growth and neurotransmission [14-16].The activities of mature BDNF are controlled by a TrkB receptor with a elevated affinity that signals development with its internal tyrosine kinase activity. TrkB receptor signal with dimerization of receptor molecules which results in intracellular phosphorylation and intracellular signaling cascades activation [17]. Subsequent studies on BDNF have suggested that a marked decrease in the levels of this specific NT is involved in the pathophysiology of numerous neurodegenerative diseases [18].The decreased BDNF concentrations in the retina can harm neurons, leading to neurodegeneration is defined experimentally. [19,20]. However, the role of BDNF in diabetic retinopathy is not fully understood yet. Regulating the levels of BDNF may be a promising therapeutic target to protect neurons and prevent T2DR. On the other hand, various microRNAs (miRNAs), that is, short noncoding RNA segments of approximately 22-nucleotides [21], have been found to modulate the expression of key genes involved in CNS neuronal synaptic plasticity, suggesting that these miRNAs regulate the expressions of BDNF during their signaling processes [22]. For gene regulation through miRNA, three mechanisms have been described as miRNA-mediated mRNA decay; direct mRNA degradation and translation repression. Recent evidence has shown a reduction in mRNA objective stabilization

through the predominately depression mechanism may be a decrease in mRNA target stability [23]. On various levels ranging from transcription and processing to target site binding and miRNA stability, miRNA activity and abundance is also regulated [24]. miRNAs have been connected to a multitude of cellular procedures and countless signals [25,26]. miRNAs works in a complex network as each miRNA could targets multiple genes, or multiple miRNAs may regulate one gene in turn [27]. Therefore, targeting one or a few miRNAs is unique opportunity for preventing the expression of multiple genes and for the development of RNA-based therapeutics. This creates a distinctive chance. MiRNAs are also recognized in many, if biological, techniques as molecules in operations with significant modulatory intervention [28]. In previous studies from several groups, alterations of multiple miRNAs in chronic diabetic patients lead to complications including diabetic retinopathy among other microvascular complications. The list includes miR200b, miR146a, miR195, mir15a etc.[29-31].However, in most studies, a particular miRNA was used to target a single mRNA. In human chronic diseases ,miR-15a family have been involved therefore miR-15a may act as a biomarker for the treatment of T2DR [32].

A. Neurodegeneration in the Pathogenesis of Type 2 Diabetic Retinopathy

Current treatments for T2DR are applicable only at advanced stages of the disease such as laser treatment, vascular endothelial growth factor (VEGF) therapy, vitreoretinal surgery and major adverse events [33-35]. Therefore, new treatments for early stages of the disease are needed. The use of multifocal electroretinograms (mfERG) has given convincing proof that brain dysfunction and vascular defects are directly related to T2DR. Thus, the growth of early microvascular defects predicts a postponed mfERG-IT period [35,36]. The implicit time in mfERG is spatially associated with retinopathy, correlates with retinopathy severity, and is a predictor for the development of visible vascular abnormalities over a 1-year and a 3-year period [37-38]. In addition, retinal diameter shift prematurely in diabetic patients and has been reported to deteriorate early in diabetic patients without structural microvascular abnormalities in the retina [39]. All these findings reinforce the concept that the neurovascular unit is altered at very early stages of T2DR [40]. Capital of developing T2DR are metabolic pathways caused by hyperglycemia, such as polyol and hexosamine pathways, the de novo synthesis of diacylglycerol-proteins kinase C (DAG-PKC), and the production of free radicals and advanced glycation end-products (AGEs) are crucial in the development of T2DR [41]. In addition, there is growing evidence that inflammatory mechanisms also have an important role in its development [42]. All of these mechanisms lead to anomalies in the cellular retina (retinal neurodegeneration). The most significant histological characteristics of T2DR are cellular apoptosis and reactive gliosis. In which neural apoptosis is followed by modifications to Glial cells called' reactive gliosis (astrocytes and Muller neurons). The three most important mechanisms in the neurodegenerative process that occurs in T2DR: extracellular glutamate accumulation; oxidative stress; and reduction of neuroprotective factors synthesized by the retina (Fig.1). Glutamate is the major excitatory neurotransmitter within the retina and it is elevated in the extracellular space under the experimental models of diabetes [44–46], similarly as within the vitreous fluid of diabetic patients with proliferative diabetic retinopathy (PDR)[47,48]. Glutamate homeostasis disorder in the diabetic retina, increased toxicity in retinal extracellular glutamate, damaging cells and triggering the T2DR growth [49–51]. Neuronal cell death is primarily caused by the inflow of calcium and sodium in cells after the glutamate activation of N-methyl D-aspartate receptors (NMDA). This produces free radicals and leads to apoptosis. [52]. Therefore, strategies to decrease the level of extracellular glutamate or to inhibit the activation of NMDA receptors may decrease neurotoxicity and cell death [51]. Another mechanism in neurodegeneration is the oxidative stress, which is critical to the growth of T2DR by aberrant manufacturing of mitochondrial-derived reactive oxygen species. Mitochondria represents the majority of endogenously shaped ROS in most tissues and are also the first to be subjected to and harmed by ROS as a result of their elevated reactivity and local production of the mitochondrial components (mainly mtDNA) are also the first to be exposed and damaged by ROS. This may cause mitochondrial energy production to drop below that required for cellular functioning, leading to loss of tissue function contributing to the onset and/or progression of retinal degeneration [53]. It was recently shown that neuronal molecules of guidance (such as neurotrophic factors) play significante functions in neuronal cell-vascular relationships to regulate the survival, development and functional retention of such cells [54–57]. Dysregulation of neurotrophical variables have been discovered in illnesses such as diabetic retinopathy to trigger neurodegeneration and pathological angiogenesis. Among these neurotrophins, BDNF is principally synthesized by the retinal ganglion cell (RGC) and encompasses a key role in retinal physiological state attributable to its antiangiogenic and neuroprotective actions. BDNF prevents oxidative stress and glutamate excitotoxicity [58,59].The downregulation of BDNF in diabetic retina therefore seems crucial in favor of neurodegeneration and can also mediate early microvascular abnormalities.

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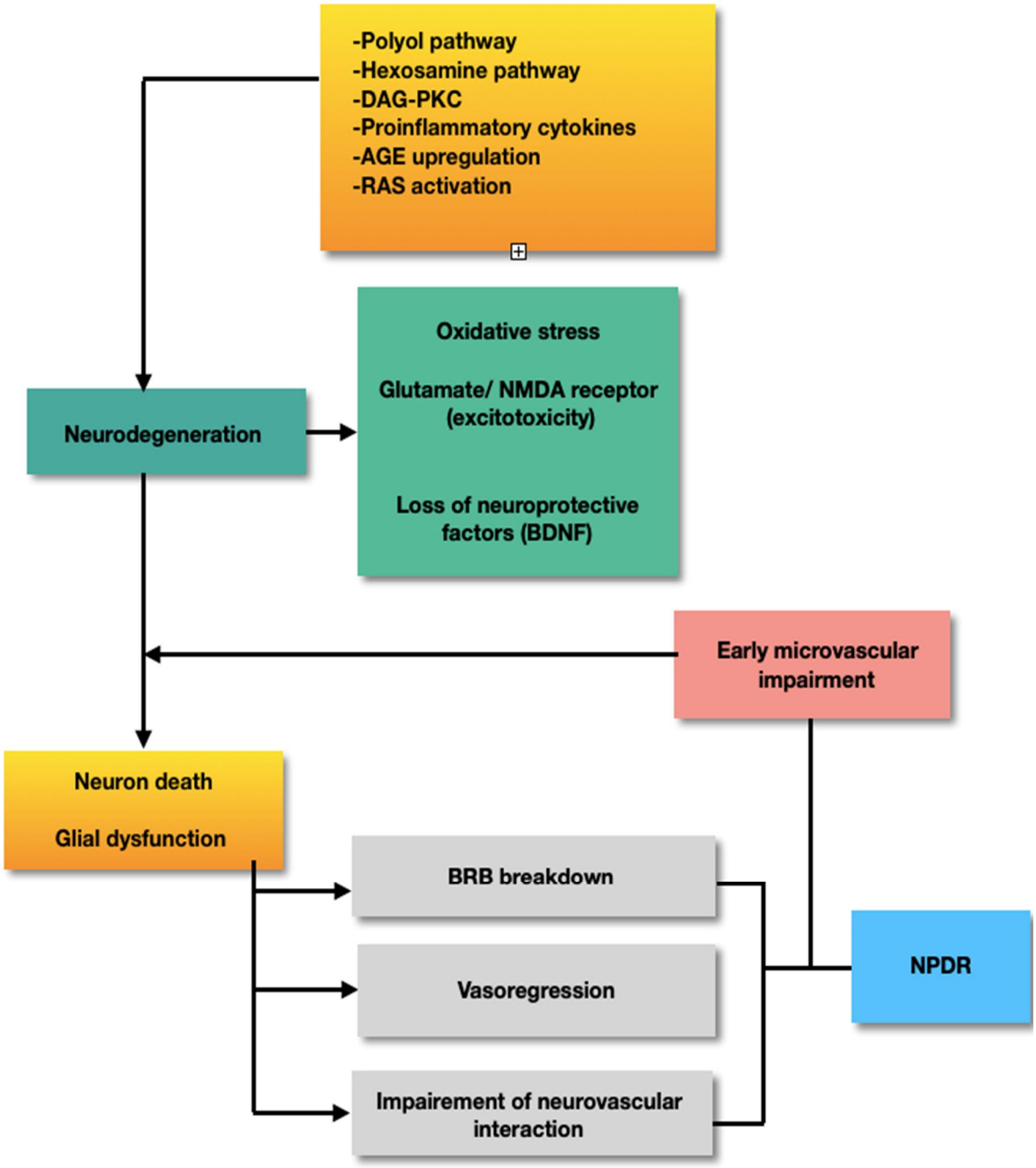

Figure.1. Schematic representation of the main mechanisms leading to type 2 diabetic retinopathy (T2DR). The hallmarks of neurodegeneration are neuronal apoptosis and glial dysfunction, whereas blood–retinal barrier (BRB) breakdown, vasoregression, and altered microvascular hemodynamic response (impaired neurovascular coupling) are the main features of early microvascular abnormalities. The oxidative stress , accumulation of glutamate and the loss of neuroprotective factors trigger in BRB breakdown, vasoregression, and impaired neurovascular coupling, thus contributing to microangiopathy and neurodegeneration. Abbreviations: AGE, advanced glycation end-products; DAG-PKC, di-acyl glycerol protein kinase C; NMDA, N-methyl-D-aspartate; RAS, renin–angiotensin system NPDR, Non proliferative diabetic Retinopathy.[60]

B. Physiology of Brain derived Neurotropic Growth factor (BDNF)

BDNF, a neurotrophical factor that is most common and widespread in the rodents ' body and distributed all over CNS [61]. As retina is a part of CNS, BDNF present in the retina abundantly. Alterations in BDNF expression have been reported to play a key role in several neurodegenerative disorder including T2DR[62]. BDNF concentrations in several liquids and tissues have been widely evaluated in people with different neuropsychiatric disorders with the majority of study suggesting BDNF is degraded in those who are not disease particular. [63]. BDNF, as in the rest of the NTs, is synthesized initially from precursor known as proBDNF, which are released to the outer cellular space and closed down by different extracellular proteases such as serine protease plasmin and matrix metalloproteinases (MMPs) for the production of mature BDNF, with the latter primarily promoting neuronal survival via activation of its specific type B tyrosine kinase receptor (TrkB) [64]. In contrast, proBDNF that does not undergo proteolytic cleavage binds to the p75 neurotrophin receptor ($p75^{NTR}$), thereby resulting in apoptosis of the neuron cell [65]. Together with the terms of either p75NTR or Trk, the selective secretion of either BDNF or mature is supposed to determine if a neuron is subjected to cell death or, in contrast, survives [66]. In addition, the p75NTR activates RhoA, a tiny triphosphate guanosine (GTPase), that prevents the neuritis elongation and causes a repulsive growth cone, indirectly indicates that matured BDNF can also be engaged in the neurogenesis, dendritic and axonal development, growth cone rotation and all are essential for the development of fresh synapses. [67]. Upon BDNF binding, TrkB dimerizes and autophosphorylates which activates tyrosine kinases that initiate signaling cascades. BDNF/ TrkB signaling provides trophic support and modulation of dendrites and synapse formation through three main pathways; mitogen-activated protein kinases (MAPK), phosphatidylinositol 3-kinase (PI3K), and phospholipase C-ɣ (PLC-ɣ) [68,69]. The second BDNF receptor and $p75^{NTR}$ has a much different function than TrkB. The $p75^{NTR}$ along with Trk receptors enhances enhances the strength of the Trk receptor for mature neurotrophin [70–72]. Alternatively, $p75^{NTR}$ can bind each of the neurotrophins directly, especially proneurotrophins [73,74]. The $p75^{NTR}$ does not have an intracellular kinase domain. Instead $p75^{NTR}$, which can create dimers, indicates signals by combining proteolytic effects with a cytoplasmic tail, and associates the effector molecules. [75-77]. Although the $p75^{NTR}$ pathway is well-known for initiating apoptosis, proBDNF activation of $p75^{NTR}$ can also cause apoptosis as well as inhibit neurite growth and spine formation [78]. Moreover, several in vitro research have proved that mortality of retinal neurons in early phases of T2DR is connected to a declining rate of BDNF, and TrkB is crucial for the defense of BDNF-induced retinal tissue cell. It is of concern, however, if BDNF will safeguard in vitro-exposed retinal tissue cells exposed to hyperglycemia by retaining the ordinary miR-15a levels.

C. Involvement of MicroRNA-15A in Type 2 Diabetic Retinopathy

MicroRNAs (miRNAs) epigenetic signaling is now a successful way to treat neurodegenerative diseases [79]. More than one-third of all protein-encoding genes are predicted to have miRNA binding sites [80]. miRNAs are a classes of short, species length of non-coding RNAs of 17–25 nucleotides and were first found at the start of the nineties in Caenorhabditis elegans [81]. Many trials have shown that miRNAs have a important effect on health and disease in the various tissues and cell kinds and the deregulated expression of these tiny rNAs. MIRNA encoding sequences represent 1–3 percent of the mammon genome; over 1900 miRNAs with critical regulatory function, including cellular growth, proliferation and distinction, have been revealed to have affected nearly all physiological mechanisms; and metabolism and homeostasis [82,83]. miRNA transcripts are generated from the transcribed stem-loop precursors and form the primary precursor miRNA. The stem loop, which is asymmetrically cleaved by the miRNA processing complex comprising the RNase III Drosha and its cofactor DGCR8, produces the precursor miRNA (pre-miRNA) in the nucleus. The pre-miRNA is transported to the cytoplasm by the nuclear transport receptor exportin-5 and the nuclear protein Ran-GTP. It is then cleaved by Dicer to produce a short duplex molecule of mature miRNA of about 22 nucleotide. These molecules are loaded by Dicer-TARBP2 complex into a member of the Argonaute protein subfamily and form the miRNA-induced silencing complex (RISC) [84]. miRNAs regulate the expression of at least half the human transcriptome by either repressing the translation of or causing the degradation of multiple-target mRNAs. The silencing mechanism may be determined by the extent of base pairing between the miRNA and the target mRNA when mRNA binds to the complimentary target sites located in the 3’ untranslated region of the target mRNA [85,86].

MiR-15a could be a key molecule within the diabetic retina tissue layer [87]. It is been reported in patients with proliferative diabetic retinopathy (PDR), higher levels of hsa-miR-15a [88]. It was also reported that miR-15a was elevated in early endothelial progenitor cells [89].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 severity of the disease increases. Under high glucose and hypoxic stress, pancreatic β-cells produce considerably much higher levels of miR-15a [90]. Some studies in animals, miR-15a expression was observed in both blood- derived exosomes and in the retina. This fact not only accentuates the role of miR-15a in the pathogenesis of T2DR, but 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 Type 2 Diabetes (T2D) advances, 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 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 [91].

D. Therapeutics of MicroRNA

Treatment based on miRNA in neuroprotection open up a new avenues for preventing or arresting T2DR development, abnormal miRNA expression is associated with many diseases. miRNAs become potential therapeutic targets and manipulation of their expression is used as new clinical treatment strategies.Restoring downregulated and blocking up-regulated miRNA expression can be achieved by using synthetic miRNA (miRNA mimic) or by inserting genes coding for miRNA into viral constructs [92,93] and the use of antisense oligonucleotides (AMO), miRNA sponges, miRNA-mask and small RNA inhibitors respectively [94-97]. Currently, the most used carriers for miRNAs delivery in vivo can be divided into two types, viral and non-viral (Fig.2).

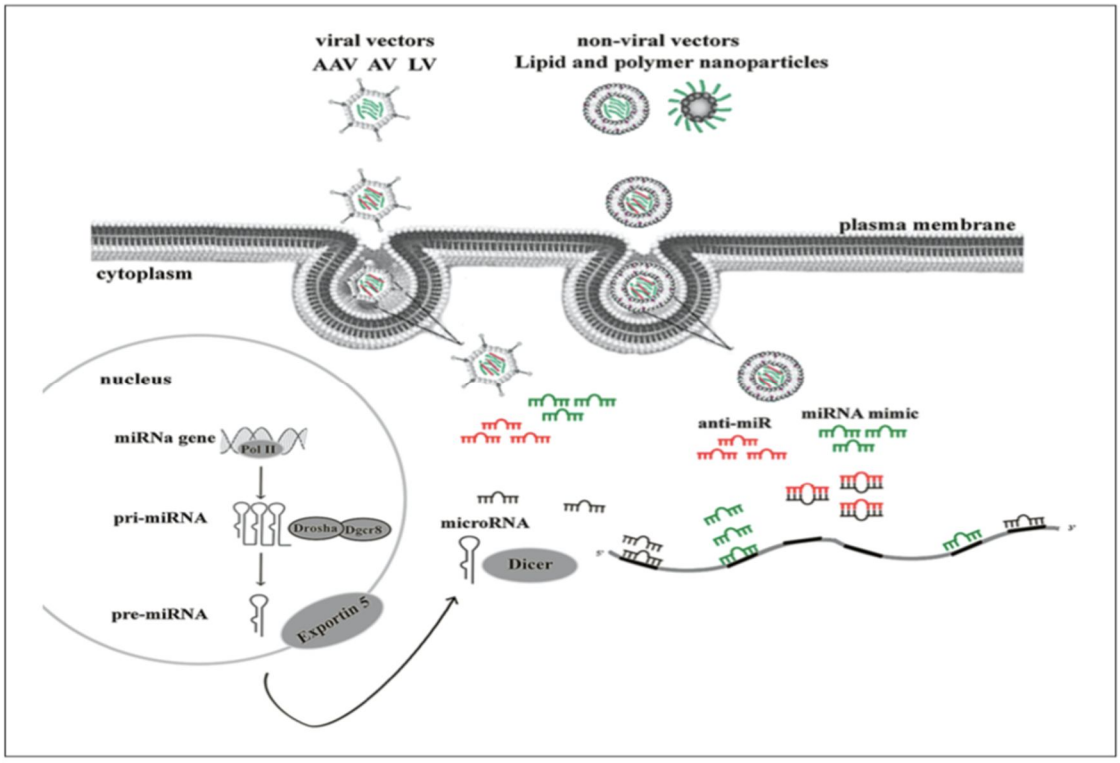

Figure.2. Existing strategies for miRNA delivery.miRNA mimics or antagomir developed in viral and/or non viral vectors are internalised in the cells by endocytosis and then they release their content still stable to replace or inhibit the miRNA function.AAV, adeno-associated virus;AV, adenovirus; LV, lentivirus.[98]

The viral-mediated delivery includes a range of viruses can be employed for these purposes, such as lentiviruses, adenoviruses, and adeno associated viruses (AAVs) [99]. Since these vectors do not integrate into the genome, yet show remarkable efficiency in transferring RNA-encoding vectors into the nucleus of mammalian cells ,even though the risk of random integration and off-target effects remains high [100]. Furthermore, the host immune response induced by the transduced viral vectors, especially by adenovirus and adeno-associated virus, occasional poor integration ,transient expression, additionally hamper the appliance of the viral delivery system [101].To resolve the limitation of the utilisation of viral vectors, non-viral vectors have becoming sensible alternatives. Lipid and nanoparticle-based delivery is the most widely and clinically advanced approach. Lipid-based delivery systems include liposomes, micro-emulsions, and solid lipid nanoparticles, among them lipid nanoparticle called stable nucleic acid lipid particles because of their lower immunogenicity, higher biocompatibility, and a more stable profile against degradation process [102, 103]. Unmodified RNAs have low biological stability and are rapidly degraded by cellular and serum nucleases, making their delivery impractical [104],furthermore the small size and negative charge associated with these RNAs inhibit their ability to cross-cellular membranes.Chemically modified nucleobases as phosphorothioate containing oligonucleotides, 2′-O-methyl-(2′-O-Me) or 2′-O-methoxyethyl oligonucleotides [105], locked nucleic acid (LNA) oligonucleotides [106], peptide nucleic acids [107], and fluorine derivatives (FANA and 2′-F) [108] could give stability to miRNAs and encourage their systemic delivery. In spite of LNA alterations have higher binding affinity, these modifications can lead to off-target effects which may cause toxicity in vivo [109]. Recently, a new compound called N,N-diethyl-4-(4-nitronaphthalen-1-ylazo)-phenylamine (ZEN), when is included at each end of the AMO, led to increased binding affinity to the miRNA and inhibited exonuclease degradation. Recent studies have shown that this group of AMOs (ZEN-AMOs) have higher potency and less toxicity than LNA-AMOs [110]. Interestingly, one clinical study has been conducted with miRNA inhibitor for the regulation of BDNF [111]. In addition to being a crucial regulator of synaptic plasticity, BDNF has also been reported to be a key element in regulating energy balance [112]. Thus, the therapeutic efficacy of increasing BDNF levels by delivering an anti-miRNA gene into mouse models of obesity and diabetes. As expected, this anti-miRNA gene transfer raised the expression of BDNF and also resulted in a marked weight loss and alleviation of obesity-associated insulin resistance [113]. It has reported that a member of the miR-15 superfamily involved in neurological diseases[114]. Regulating level of miR-15a using anti-miR can fulfil the purpose [115]. 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.

II. CONCLUSION

The central role of neurodegeneration in the pathogenesis of T2DR is a solid basis for proposing BDNF as an Neuroprotective for preventing T2DR.The use of miRNA inhibitors to target the miRNAs that downregulates the expression of BDNF holds prospects of restoring BDNF based repair in neurodegeneration in T2DR, but much more research is needed. Additionally, the discovery of miRNAs and their expression profile in a wide variety of diseases has led researcher to understand the featured role of miRNAs as biomarkers during disease progression. Furthermore, because the miRNAs are relatively small size and they can regulate the network of target genes, they are promising targets for miRNA based therapy. The most considerable feature of miRNA therapeutics is that a single miRNA (miR-15A) could be useful for targeting multiple genes that are deregulated in disease, which can be further investigated through systems biology and network analysis that allows designing disease-specific personalized therapy. In summary, miRNAs are poised to provide diagnostic, prognostic, and therapeutic targets for several diseases. As the field continues to rise, miRNA-based therapeutics may develop a novel class of drugs for different diseases.

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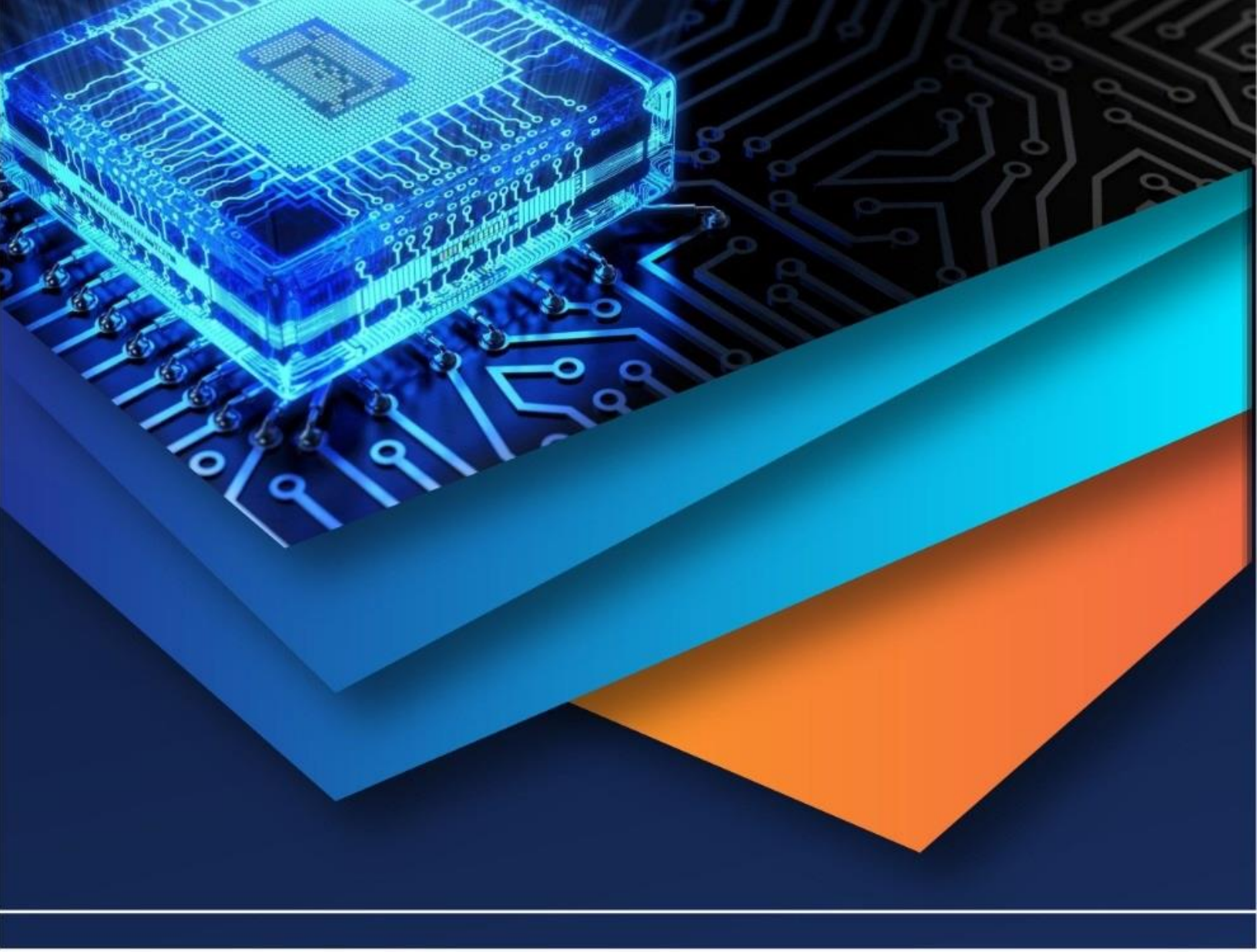

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