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Histone Lysine Methylation: A Potential New Treatment Target with Respect to BDNF Gene in Type 2 Diabetic Retinopathy

Shreya Priyam[1], Vaishnavi Gupta[2], Moumita Das[3], Archana Tiwari[4]
[1, 2]*Students,* [3]*Scientist, School of Biotechnology, Rajiv Gandhi Proudyogiki Vishwavidyalaya (State Technological University of Madhya Pradesh), Bhopal, Madhya Pradesh, India.*
[4]*Head of the Department, School of Biotechnology, Rajiv Gandhi Proudyogiki Vishwavidyalaya (State Technological University of Madhya Pradesh), Bhopal, Madhya Pradesh, India.*

Abstract: ***Type 2 diabetic retinopathy (T2DR) is a highly developed manifestation of diabetic retinopathy along with a prominent cause of sightlessness on a global scale. Brain-derived neurotrophic factor (BDNF), which is an associate of neurotrophin family of proteins and enciphered by the BDNF gene is very effectual in shielding retinas from abnormally high blood sugar associated with diabetes in-vitro. Till date, very less number of facts with respect to epigenetic modification is known in T2DR and future aspect associated with epigenetic studies can be explored in this slow progressing disease. Epigenetics have now turned out to be a crucial field of study in bioscience experimentation which regulates gene expression and change their function without any alteration in the DNA sequence in diabetic environment. Histone lysine methylatio take part in alteration of chromatin structure and regulation of gene expression. After going through the available literature, it can be hypothesized that by regulating H3K9 methylation which is a repressive mark, expression level of BDNF can be regulated which in turn can normalize the BDNF-TrkB signaling pathway and may protect apoptosis of human retinal cells in T2DR promoting their survival. mechanizable approach into histone modification may provide the mode for therapeutic function of drugs in T2DR. The present review is focused on histone methylation (H3K9) with respect to BDNF gene expression related to pathogenesis in T2DR and might be helpful for therapeutic purpose.***

Keywords: Epigenetics, BDNF (Brain derived neurotrophic factor), H3K9 methylation, Type 2 Diabetic Retinopathy.

I. INTRODUCTION

Diabetes and disorderliness linked to metabolism are primary beginning of micro plus macro vascular hurdles of diabetes accounting retinopathy, nephropathy, and neuropathy [1]. Till date many studies has been done in the field of diabetic retinopathy and its pathogenesis, but still there are very few therapeutic options. T2DR (Type 2 Diabetic Retinopathy) is a high level vascular hindrance of both type-I and type-II diabetes [2]. T2DR, one of the problems of diabetes is a foremost reason of loss of sight worldwide. The characteristics of chronic inflammatory disease, microvascular and neurodegenerative disease has been found in T2DR. The damaged microvasculature retina is a hallmark of this disease [3]. About ninety three million people suffer from diabetic retinopathy worldwide; seventeen million suffer from proliferative diabetic retinopathy and twenty eight million with vision frightening diabetic retinopathy [4]. There are about 4.8% cases of blindness related to the disease and it is estimated that by 2030 this would raise to 191.0 million from 126.6 million in 2010. The prevalence of type 2 diabetes (T2DR) is escalating at a distressing speed; approximately 80% of diabetes patients after 15 years develop retinopathy [5].

Diabetic environment is responsible for up or down regulating many genes in the retina, and promising study revealed that epigenetics has now become one of the key player associated with the gene regulation and its function. These epigenetic changes can be affected by number of circumstances including age, atmosphere, disease condition and lifestyle. Epigenetics also recognized as “prefix genetics,” “external genetics,” or “post-genetics,” involves the change in the function of gene without any alteration in the DNA sequence [90]. These modifications are associated with the advancement of different diseases counting autoimmune diseases, cancer, psychiatric diseases, addictive diseases and neurodegenerative diseases. Three main epigenetic modifications which contribute in the change of function of gene without any change in the base sequence of DNA are DNA methylation, chromatin remodeling, histone modifications and RNA that do not code. These “epigenetic” modifications be reversible, as well as can be passed from generation to generation [6], [7]. Epigenetic changes contribute in the pathogenesis of diabetic retinopathy by playing a key role in pathologic responses such as neurodegeneration and inflammation which contribute to the development of diabetic retinopathy. Latest studies indicate that change due to epigenetic modification in the genome can lead to disease onset [8].

BDNF is crucial in memory-associated neuroplasticity modification, cell survival proliferation, regulation and synaptic growth in the central nervous system (CNS). It also assists the survival of neurons present in the area. Repressive histone methylation mark (H3K9) is accompanied with the suppression of any gene. There is downregulation of BDNF in case of T2DR. Targeting histone lysine methylation may appear fruitful in the prevention of T2DR to some extent.

II. DIABETIC RETINOPATHY: PATHOGENESIS

Hyperglycemia which is observed as the driver in the advancement and the progression of diabetic retinopathy results in the damage of diabetic retina in the oxidative stress environment. Endothelial cells lining microvasculature and retinal microcirculation gets activated and produces cytokines foremost to the production of mediators responsible for inflammation which contribute into the development of diabetic retinopathy. Hyperglycemic condition inside the cell increases the flux through different pathways like protein kinase C pathway (PKC), polyol pathway, reactive oxygen species (ROS) production, advanced glycation end product (AGEs) and vascular endothelial growth factor (VEGF). High level of glucose increases de novo production of diacylglycerol (DAG) which is the principle activating agent of PKC. PKC pathway is a serine/threonine kinase pathway consisting of ten enzymes out of which beta1/2 isoform is closely associated with the pathological process of Diabetic Retinopathy- contrastive production of extracellular matrix (ECM) proteins, high production of VEGF which is a angiogenic factor, advanced glycation end product (AGEs). Elevated production of VEGF is related to the blood tissue barrier breakdown and development of new blood vessels in the hypoxic condition of cells leading to proliferative DR. High level of AGEs in the blood vessels of retina of diabetic individual are considered as vital mediators for pathogenecity in diabetic problems including retinopathy. Early glycation (non enzymatic glycation between glucose and amines residues of lipids, nucleic acids and proteins) & oxidation leads to creation of schiff base, then to amadori product and finally formation of AGEs which is toxic. The interaction of AGEs with precise receptors present on cell surface like galectin-3, CD36, RAGE and macrophage scavenger receptor is coupled with the progress of DR. Aldose reductase metabolizes excess glucose to sorbitol and sorbitol dehydrogense finally results in the conversion to fructose and NAD^+ as cofactor in polyol pathway. In case of diabetic hyperglycemia, due to excess production of sorbitol and reduced level of cofactor results in reduced level of glutathione (free radical scavenger),leading to oxidative damage of retinal cell [16].

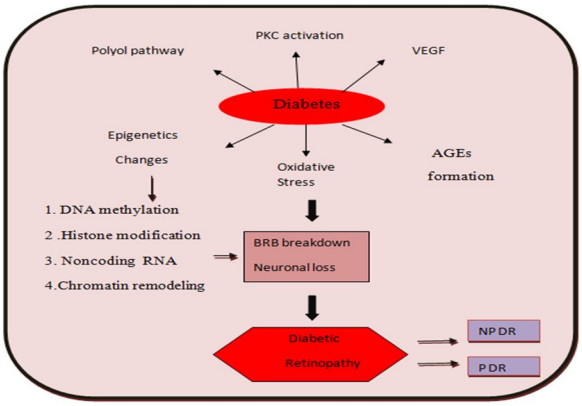

Figure 1: Epigenetic changes in Diabetic Retinopathy. BRB: Blood retinal barrier, NP DR: Non Proliferative Diabetic Retinopathy and PDR: Proliferative Diabetic Retinopathy.

III. TYPE 2 DIABETIC RETINOPATHY

Type 2 Diabetic Retinopathy is a disease which involves complications in the retina due to diabetes. Epigenetic modifications act as a bond between environmental and genetic factors in disease development. In Type 2 diabetes, an individual develop insulin resistance in insulin-targeting tissues, mainly the skeletal muscle, liver, and adipocytes [9]. Epigenetic changes associated with metabolic abnormalities such as obesity, dyslipidemia, hyperinsulinemia, are often linked with T2DR [9]-[12]. Retinopathy is categorized into two according to the harshness and development of disease; Non-proliferative diabetic retinopathy (NPDR) and Proliferative diabetic retinopathy (PDR). PDR, an advance stage of retinopathy is identified by neovascularization and Non-proliferative diabetic retinopathy (NPDR) is identified by high vascular sponginess. PDR and NPDR results in the oxygen deprivation condition in the retina.The initial effect of this slowly developing disease comprise embrace microaneurysms, hemorrhages, cotton spots, intra-retinal-microvascular abnormalities, and blood vessel hemorrhage. However, in additional advanced stages, fresh blood vessels are produced in the retina and on the posterior surface of the vitreous, and to extreme condition lead to the aloofness of the retina, resulting in vision defect [3], [13], [14].

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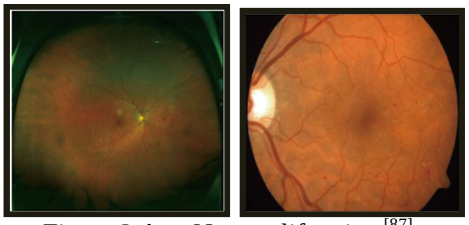

Figure 2 A : Non proliferative [87].

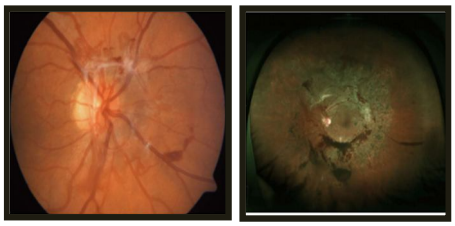

Figure 2B: Proliferative Diabetic Retinopathy [87].

The potential links between hyperglycemia and DR has been known through invivo and invitro studies of five major biochemical pathways .They are polyol pathway, hexosamine pathway, advanced glycation end products (AGEs) pathway, Poly (ADP-ribose) polymerase activation and protein kinase C pathway[14],[15]. These pathway together contribute in the production of oxidative stress (OS), micro vascular dysfunction, inflammation, and mitochondrial injury, that successively up regulate pro-inflammatory mediators, chemokine's, transcription factors, and adhesion molecules.[16] OS act as a pivotal role player in the growth of microvascular and diabetes problems of cardiovascular , which leads to blood- retinal breakdown thereby upregulating pro-angiogenic factors leading to proliferative diabetic retinopathy(PDR)[1]. Recent findings showed that abnormal function and retinal neurons death in DR ends up in failure of distinction sensitivity, difference in color discernment,illustration deformity and unusual variation. Studies have suggested that BDNF factor shows chief role in aldohexose (glucose) and macromolecule (lipid metabolism) and inflammation [18], [19]. DR has now became the foremost reason for visual disorder among the operating population owing to its high rate of inflicting visual disorder and vital healthiness issues.

IV. THE BRAIN DERIVED NEUROTROPHIC FACTOR

The BDNF gene in human is found on short (p) arm of chromosome eleven at position 14.1 (cytogenetic Location: 11p14.1) and is 70 Kb in size. BDNF gene consisits of eleven exons (I–V, Vh, VI- VIII, VIIIh, IX), out of that exon IX and I-VII contain purposeful promoters. Exons II, III, IV, V, Vh, VI, and VIIIh don't have any translation begin site therefore translation of these exons starts from the ATG of exon IX. All BDNF mRNAs include the sequence for the pro-BDNF protein, coded by exon IX [20], [21]. BDNF performs its function through two different receptor systems, tropomyosin-related kinase B (TrkB) receptor (high affinity receptor) and p75 (small affinity receptor) is a non-specific receptor for entire neurotrophins.

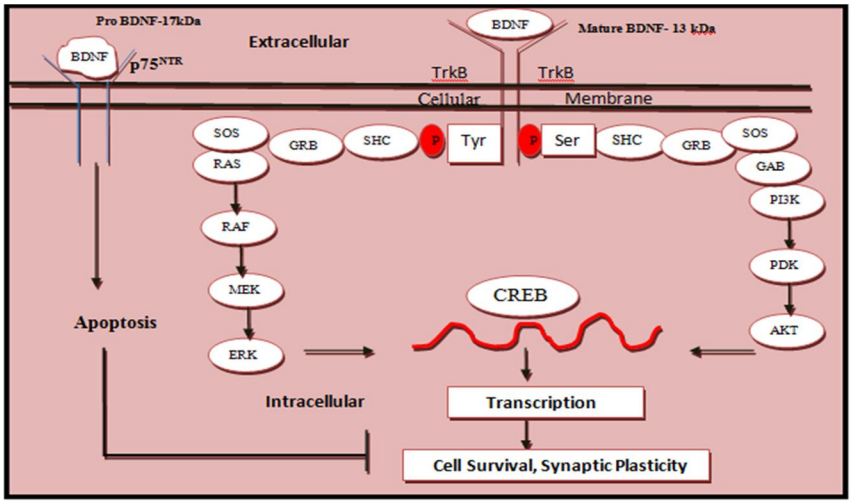

Figure 3: BDNF-TrkB Signalling Pathway for Cell Survival.

They are involved in different functions of brain comprising neuronal connectivity, memory formation, growth of neurons that are immature & endurance of mature neurons. BDNF/TrkB signaling (Ras-Raf-MEK-ERK pathway, additionally referred to as MAPK pathway) is crucious for growth, differentiation and survival of cells and neurons in retina [22].

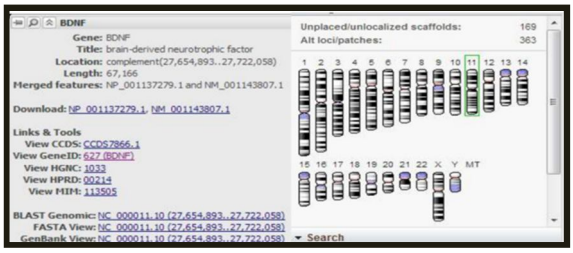

Figure 4: Length (in base pair) & Localization of BDNF Gene on Chromosome Eleven.
(https://www.ncbi.nlm.nih.gov/genome/gdv/browser/?context=gene&acc=627)

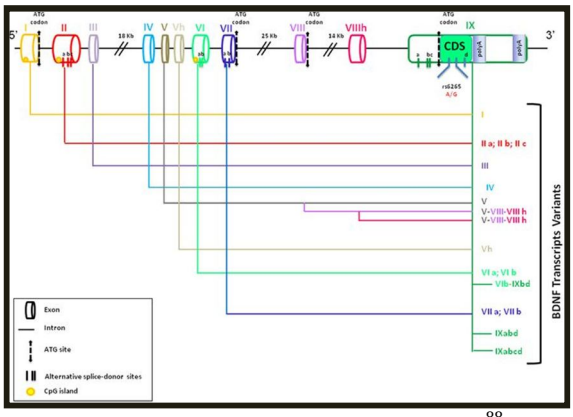

Figure 5: Human BDNF gene structure [88].

Nerve growth factor (NGF) was discovered in 1950s because of its organic process (endurance and growth-promoting) consequence on sympathetic and sensory neurons. Brain-derived neurotrophic factor (BDNF), component of the "neurotrophic" family, was found in pig brain in 1982 [23]. After this, new members of neurotrophin such as neurotrophin-3 (NT-3) in rat & human [24] and neurotrophin-4/5 (NT-4/5) in xenopus and viper [25]-[27]. Were found. Later on, rat & human NT-4 has been isolated with the help of particular sequences of NT-4 xenopus and viper.These family of neurotrophin in the central & peripheral nervous system affects populations of neurons [26].

In vivo and in vitro work revealed that Brain- derived neurotrophic factor have an impact on cell growth, segregation plasticity, synaptic connectivity and finally endurance of cells in brain and neuronal cells [28]-[31]. In one of the study by Rohrer et al, it was revealed that differences in retinal function is triggered by the nonappearance of Brain-derived neuotrophic factor or its receptor [32]. A study also revealed that BDNF in oxidative stress conditions in rodents diminishes injuries of ganglion cells present in retina after the injury of optic nerve and protect neurons. Another study revealed the effective role of Brain- derived neurotrophic factor in the endurance of ganglion cell present in retina in cats with broken optic nerve [33], [34].

V. BDNF VS TYPE 2 DIABETIC RETINOPATHY

Type 2 diabetic retinopathy (T2DR) which ultimately leads to blindness in developed countries is nowadays an important area of research [35]. T2DR patients have been found with reduced level of BDNF in retina when compared to normal non diabetic individual [36]. In vivo studies so far demonstrated that during the initial stage of T2DR, death of retinal neurons is associated with the reduction of BDNF and TrKB receptor protein. These receptor proteins are induced by BDNF and are essential for protection of the retinal cells. This difference along with epigenetic modification, genetic variations bring to the platform that somewhere BDNF could also be concerned in hypoglycemic agent (insulin) resistance and within the pathological process of T2DR, altering TrKB receptor [37]. A study in animal model demonstrated that during initial stage of T2DR, necrobiosis of retinal ganglion cells (RGCs) occur and at the same time lack of BDNF is associated with retinal neuro-degeneration. It has also been found that BDNF during early stages of T2DR inhibits apoptosis of retinal ganglion cells of rat. On the other hand, the exact procedure by which BDNF modulates RGCs remains elusive [38]. Previous studies showed that BDNF supports regeneration of nerve fiber and retinal neurons

[39], [40]. BDNF also have been found to take the lead function in the regulation of conjunction agility. Regulation of conjunction plasticity is thought to be associated with the knowledge & remembrance in the brain of adult. Clinical studies in dog model of DR demonstrated that good glycemic control for several years can help block DR progression but the effect is not fast. Since, DR is a slow advancing disease and during disease recovery in the middle if good glycemic control is lost, it can lead to phenomenon ''metabolic memory''. However, it is still not clear whether good glycemic control help in the early prevention and treatment of T2DR [41]. Several studies in mice model demonstrated the presence of metabolic memory which showed proper glycemic management after improper glycemic manage could not sufficiently block microvascular dysfunction [42] .Therefore, it confirmed that vascular alteration occurs early in DR and also maintains metabolic memory.

VI. EPIGENETIC MODIFICATION: DNA METHYLATION AND HISTONE MODIFICATION

Epigenetics refers to heritable and stable change which changes the function of a gene without any alteration in the base sequence of DNA. This may turn any gene on or off depending on the target site. The two major epigenetic modifications include histone modification and DNA methylation which is related to disease and also serve as biomarker in the progression of disease. Epigenetic changes remodel the chromatin organization that influences the interaction of transcription factors thereby modulating the expression of gene. Chromatin is a composite structure of histones & nucleic acids (nucleosomes). DNA winds around four histone proteins – histone 2A & B, H3 & H4 and forms a tetrameric structure. Inspite of complex packing of DNA, histone at its N-terminal tails are prone for post translational modifications such as acetylation, methylation, sumoylation phosphorylation & ubiquitination [43]-[46]. All epigenetic changes are not permanent, but their continuous response to change in environment such as diabetes and their heritable nature, make them potent targets for chronic region of most genes. However, exact mechanism of epigenetic modification within DR still remains evasive. ''Histone code theory'' states that various histone modifications in specific promoter region specify a particular epigenetic state that results in gene suppression or activation [47]. Thus, histone modification pathways can directly or indirectly affect gene transcription by altering chromatin structure of effector complexes. Most of the genes present in the retina of human & mouse such as Set7/9 encode histone modifying enzymes and elevated expression in the retina of adult mouse depend on positive regulative domain sixteen [48].Several genes like Ezh1, Ezh2, Prdm8 and Mecom, code histone methyltransferases and also show active expression patterns through progression thereby play a vital role in retinogenesis [49]. DNA methylation is an adding up of a methyl group on location five of cytosine residues on CpG islands within the genes promoter region, related with gene suppression by oppression of the transcriptional machinery.DNA methyltransferase (DNMT) enzymes comprise 5 members Dnmt1, Dnmt2, Dnmt3a, Dnmt3b and Dnmt3L catalyze the process of DNA methylation. Among the five members of DNMT, Dnmt3a, Dnmt1 and Dnmt3b are catalytically active. DNMT1 functions in copying and maintainance of methylated cytosine from parent to daughter cells during replication at S phage. DNMT3a & DNMT3b are implicated in de novo DNA methylation of unmethylated CpG dinucleotides. These modifications alter DNA- protein interaction thereby changing chromatin structure leading to suppression of genes [50]-[52]. Thus, understanding the function of epigenetic regulators within the pathological process of diabetic retinopathy might facilitate establish novel targets of the unwellness that is the foremost explanation of vision defect in young adults. The key play of epigenetic modifications in the pathogenesis of diabetic retinopathy is an emerging area of research. In contrast to DNA methylation histone methylation is poorly understood. The principle histone methyltransferases involved in histone methylation and associated with repressive mark are G9a (catalyze H3K9 monomethylation to di-methylation) and SUV39H1 (catalyze H3K9 dimethylation to tri methylation). G9a is the major euchromatic H3K9 histone methyltransferase in mammals. Histone methylation can take place on different histones but methylation on H3 and H4 are more common. Histone methylation can cause the gene either to express or suppress depending upon the site on which the methylation takes place. For example, methylation of H3K9 (Histone 3 Lysine 9) result in gene suppression [53].

H3K9 di-methylation suppresses gene expression through employment of DNA methyltransferase enzymes that intercede methylation of CpG dinucleotides that then engage repressive chromatin remodeling complexes [54]. Since it is well-known that deoxyribonucleic acid methylation methylation could act in synchroneity with histone modifications resulting in additional tight regulation of gene expression, a study was done to investigate epigenetic connection between alcohol and cannabinoid activity in association linking histone modification and DNA methylation. For instance, DNA and histone methylation together may form transcriptionally inactive chromatin which results due to binding proteins like MeCP2 that afterwards binds to DNA that is methylated which results in the interaction of HDAC enzymes with the methylated promoters ensuing silencing of gene [55].

In vitro and *in vivo* studies showed that DNMT1 directly bind G9a during DNA replication in the nucleus. Thus, direct physical association linking G9a and dnmt1 impart a possible method of synchronized deoxyribonucleic acid and histone 3 lysine nine methylation on euchromatic regions in in-vivo throughout replication (cell division). The mass of H3K9me2 was in shut proximity

to G9a and DNMT1 as proven by a minute spots colocalization pattern. Thus, throughout cell division DNMT1, G9a, and H3K9me2 are present in the locality of DNA synthesis [56]. Gene interruption of G9a considerabl decrease H3K9 methylation in euchromatic regions in mice. In other study, it was confirmed that anti-apoptotic existing gene repression induced by doxorubicin occur by DNA and histone methylation of its proximal promoter, that is mediated by the physical staffing of DNMT1 [57], [58].

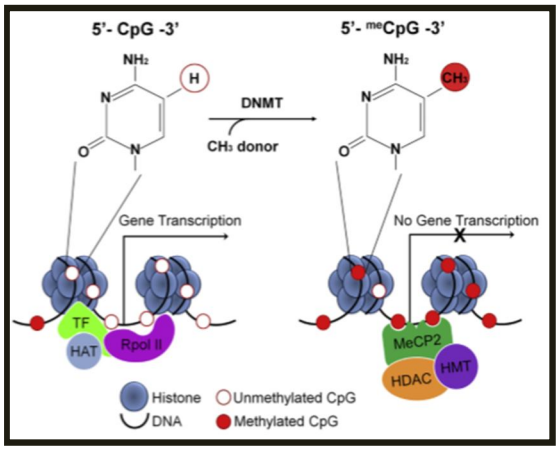

Figure 6: CpG sites in methylated Promoter region of gene employee's chromatin silencing complex histone deacetylase (HDAC) and histone methyltransferase (HMT) and DNA binding proteins such MeCP2 that ends up in gene suppression [89].

VII. HISTONE METHYLATION

Histone methylation was first illustrated in the year 1964 [59]. Histones are capable of mono-, di-, or trimethylated on arginine and lysine residues (most common) on N-terminal tails of histone. The most highlighted methylated sites in H3 include lysines 79, 36, 27, 9 and 4, lysine 20 in H4. Unlike phosphorylation, acylation, and methylation marks don't alter the charge of proteins however function tying up docking sites for specific binding proteins called histone readers. Histone methylation is related to gene repression or activation counting on which residue is modified; normally, methylation at H3K36, H3K4, and H3K79 correlates through gene transcription, while methylation at H3K9, H3K27, and H4K20 correlates through transcriptional repression [60], [61]. Methylation of a lysine residue was 1st reported in the flagellin protein of *Salmonella typhimuriumin* in 1959 by Ambler and Rees [62], [63]. Histone methylation is typically thought as stable epigenetic mark and is catalyzed by methyltransferases (HMTs) & demethylases (HDMs), which increase the complexity of the histone methylation within the pathological process of diseases and diabetic complications. Usually H3K9me are often mediated by SUV39H1/2 (suppressor of variegation 3–9 homolog 1/2), G9a, GLP (G9a-like protein), SETDB1/ESET (SET domain, bifurcated 1/ERG-associated protein with SET domain), and Eu-HMTase1 and is related to gene suppression [64]-[68]. Now it is identified that methylation of lysine is mainly a constant epigenetic changes; it can be reversible by histone demethylase. The primary known histone demethylase is essential amino acid lysine demethylase1 (LSD1), which may specifically take away H3K4me and H3K9me marks. Recently, a great deal of lysine demethylases are known with varied specificities for various histone lysine residues whose terminology has been modified to lysine demethylases (KDMs) [69]-[71]. Furthermore, methylation H3K9 methylation is reversible and shown to regulate gene expression [72]. Several recent reports showed that histone methylation could also be accountable for the "metabolic memory" development resulting in long changes in diabetic complications together with DR.

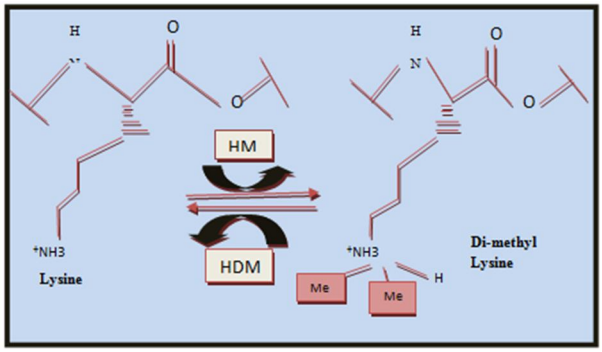

Figure 7: Methylation & Demethylation on Lysine Residue.

Lysine methylation is accompanied with numerous cellular processes together with cell fate determination, terminal differentiation and cellular signaling pathways. The MAPKs regulate various cellular processes, together with cell proliferation, cellular differentiation, cell migration and survival, in response to extracellular signals. Aberrant regulation of those MAPKs is also related to numerous pathological conditions, as well as cancer.Recent studies have shown that arginine and lysine methylation also regulate the activities of MAPKs [73]-[75].

In invitro study of rat model, effects of inhibition of the repressing H3K9 histone methyltransferases SUV39H1 and G9a (responsible for H3K9 methylation) on neuronal survival and shelter in O_2 glucose deprivation atmosphere (OGD), BDNF gene expression was upregulated around promoter I, II and III selected in cerebral ishchemia [76]. Hypoxic environment in cancer cells are related with the initiation of methyl transferase G9a activity inhibiting demethylation. The hypoxia-mediated H3K9 methylation typically results in suppression of tumor suppressors together with RUNX3, BRCA1, RAD51, and MLH1. Moreover, 2HG mediated in hypoxic environment also inhibits the work of KDM4C to promote H3K9 methylation, altering gene expression in cancer cells [77], [78].

So, targeting H3K9 methylation in cancer could turn around the modification of gene expression and decrease oncogenic result of hypoxic condition in cancer.

However, till date not much studies done on histone lysine methylation in relation to T2DR. Recent studies revealed the regulation of chromatin structure in the nervous system due to histone methylation [79]. H3K9 di-methylation also leads to repression of gene in rat hippocampus during consolidation of fear. Thus, active repression of transcription which depends on histone methylation functions as a key player within the consolidation of discourse recollections [80].

Brain-derived neurotrophic factor (BDNF) plays a role in mediating molecular, cellular, and behavioral adaptations underlying drug addiction. A study confirmed the association of histone H3 methylation in the regulation of BDNF gene expression around promoter II and III in the ventral tegmental area (VTA) and locus coeruleus (LC) of rats during enforced abstention of morphine. The result showed downregulation of BDNF which can revert back after exposure to inhibitor, inhibiting methyltransferase activity [81]. However, exact mechanism still remains elusive.

A suppressive histone mark H3K9me3 which is generated by G9a histone methyltransferase, is expressed in the mouse retina through progression. Inhibiton of G9a in the progenitor cells of retina results in the loss of H3K9me3 thereby leading to up-regulation of number of genes [82]. H3K9 methylation is also associated with reduction in the remembrance related to BDNF in response to stress during aging in Alzheimer disease (AD) [83]. Therefore, histone methylation being stable histone modification may represent a potent target in the Therefore; histone methylation being stable histone modification may represent a potent target in the therapeutic study of Type 2 diabetic retinopathy with respect to BDNF gene regulation.

VIII. HISTONE MODIFICATION IN RELATION TO DIABETIC RETINOPATHY

Diabetic retinopathy is a multifactorial, slow progressing disease which continues to progress after control of hyperglycemia and associated with a number of metabolic abnormalities. Epigenetics could be one of the important actor in the disease growth and progress of DR, but still it is in its infant stage. Another study showed that diabetic condition results in epigenetic modification of number of genes associated with DR pathogenesis as well as presence of enzymes involved in epigenetic changes. SUV39H2 is a gene that encodes histone methyltransferase which catalyzes the methylation of H3K9. In Finnish Diabetic Nephropathy Study with ~3000 diabetic patients, SUV39H2 polymorphism associated with diabetic microvascular complications was found, counting retinopathy, which suggested the function of histone modifications in diabetic retinopathy growth and progression [84]-[86].

IX. THERAPEUTIC UTILITY: THERAPIES TARGETING EPIGENETIC MODIFICATION

The suppression of genes can be easily altered with the help of epigenetic factors in persistent diseases. As mentioned above, histone methylation (H3K9), a stable epigenetic repressive mark associated with gene repression can provide insights into diagnosis and prognosis of T2DR. Thus, H3K9 methylation of genes associated with the disease can be an important target for particular drug treatments. Histone modification can alter gene expression thereby increasing chances of disease and the process can be easily homeostatically controlled by group of cellular enzymes that add methyl group or vice versa. Hence, from available literature reviewed, H3 methylation is in its infant stage and this review is basically focused on H3K9 methylation and demethylation with respect to BDNF gene which might help in the prevention of T2DR.

X. CONCLUSIONS

Experimental studies together with cell and animal models likewise as clinical studies have discovered damaging results of hyperglycemia with the development and progression of DR, less therapeutic approaches are incontestable. Brain-derived neurotrophic factor functions as a principle player in protecting the cells of retina from apoptosis, supporting their survival and differentiation. However, impact of epigenetics in DR has come up as an promising part of research, where conversion of epigenetic changes back to its position may provide a new approach for DR hindrance and treatment. H3K9 methylation is a dynamic method which can turn on or off genes and may play a significant function in gene deregulation associated with T2DR. H3K9 histone methyltransferase as a target could provide some therapeutic benefit to repeal the unusual gene expression, thereby upregulating BDNF. Deciphering this association represents a step toward untangling the regulatory network that accompanies diabetic complications which can help in increasing BDNF levels in diabetic retinal cells to some extent. This could be a new therapeutic target in T2DR. Like HDACs inhibitors are shown to be a unique category of therapeutic agent in DR, evidences showed that inhibitors of HMTs could also be new therapeutic agents for T2DR in the future studies.

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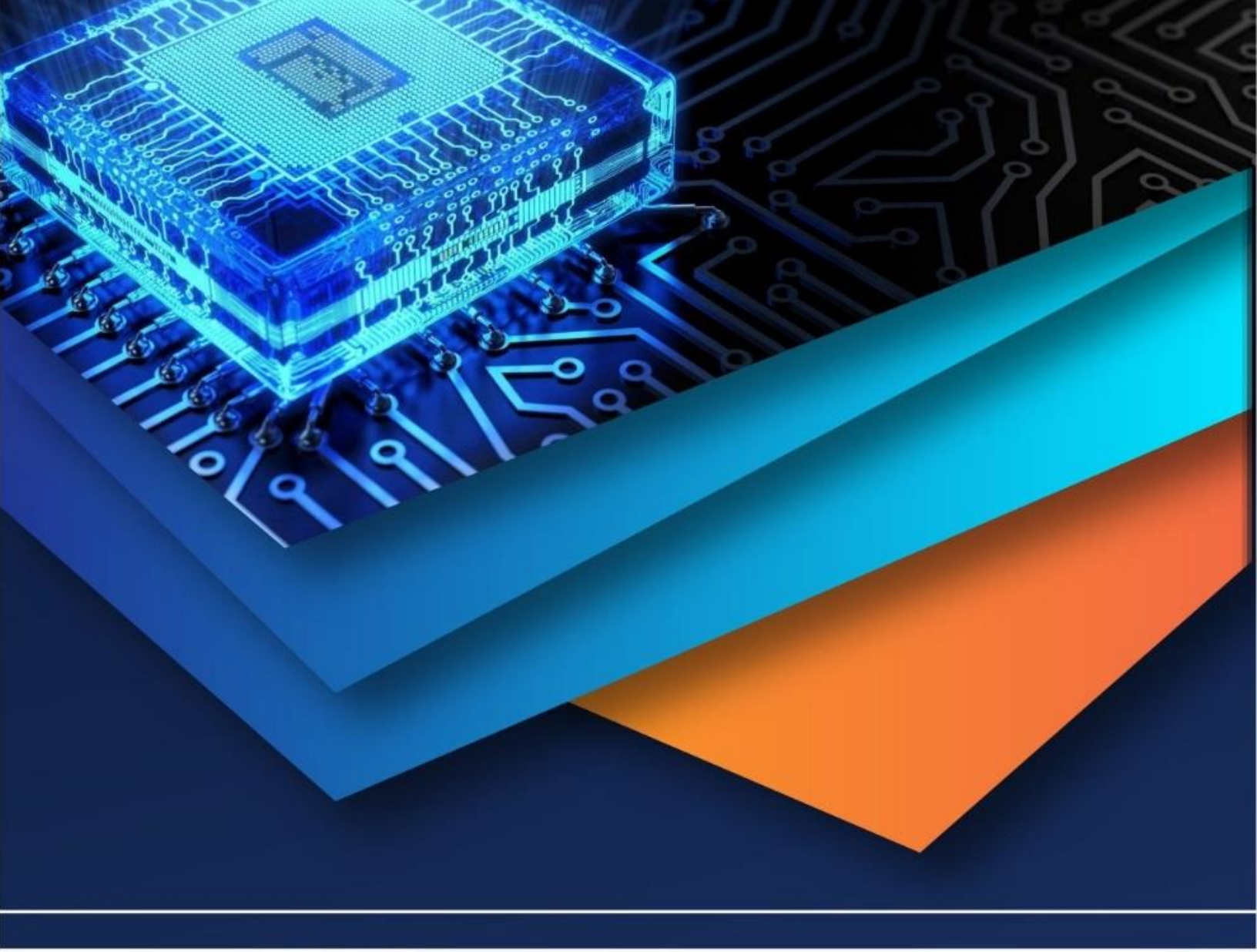

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