

Epigenetic Modification Through Acetylation In BDNF Gene & Potential New Treatment Targets In Type 2 Diabetic Retinopathy.

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ABSTRACT: Type 2 Diabetic retinopathy, the most common diabetic eye disease, occurs when blood vessels in the retina change. Type 2 Diabetic retinopathy has emerged as a major public health concern. The environmental factors, lifestyle or disease process can also bring in modifications in the DNA, and these epigenetic modifications either silence or activate a gene without altering the DNA sequence. Diabetic environment up- or down regulates a number of genes in the retina, and emerging research has shown that it also facilitates epigenetic modifications. Brain-derived neurotrophic factor (BDNF) encoded by the BDNF gene is effective in protecting retinas from hyperglycemia in-vitro. In Type 2 Diabetic retinopathy chromatin remodeling, H4 level of BDNF gene can be analyzed through the acetylation level, and might be possible to revert back to normal. This process (acetylation) can control Type 2 Diabetic retinopathy. Hence the idea of this review was to define the role of Acetylation and Deacetylation on BDNF gene with respect to Type 2 Diabetic Retinopathy. Through epigenetics modification, lesser known facts can be explored about this disease and the future possibilities can be looked through the glass of epigenetic studies. With epigenetic modifications playing an important role in diabetic retinopathy, it is now becoming critical to evaluate these modifications, and understand their impact on this slow progressing blinding disease.

KEYWORDS: Epigenetics, BDNF (Brain-derived neurotrophic factor), Acetylation H4, Type II Diabetic Retinopathy.

I. DEVELOPMENT OF TYPE 2 DIABETIC RETINOPATHY

Type 2 Diabetic retinopathy (T2DR) is the most common diabetic eye disease, or one of the major microvascular complications affecting the vision, and is the leading cause of blindness in working age adults. It occurs when blood vessels in the retina change. Sometimes these vessels leak fluid or even close off completely and renders it a leading cause of preventable blindness (1,2). T2DR is associated with neurodegeneration and apoptosis may occur in diabetic retinas. Recent progress in understanding of Type 2 Diabetic retinopathy pathogenesis has led to significant advances in available pharmacotherapy, however, a cure for T2DR is yet to be realized. Biochemical alterations such as oxidative stress, activation of protein kinase C and formation of advanced glycation end products have been detected as a response of the retina to hyperglycemia(3). With recent progress in the management of diabetes, fortunately, the macrovascular mortality is declining, but, diabetic patients are living longer and the incidence of retinopathy and loss of vision associated with this is increasing. Worldwide, approximately 93 million people have diabetic retinopathy, which includes 17 million with proliferative diabetic retinopathy and 28 million with sight threatening diabetic retinopathy. As the incidence of diabetes is increasing at an alarming rate, in 2030, ~155 million of diabetic patients are projected to have retinopathy, with more than 51 million among them facing vision-threatening retinopathy(4). Early detection and treatment remain the gold standards for its management. In the last two decades, we have seen around 90% of young adult blind patients because of Diabetic Retinopathy. Worldwide this disease hampering our society with almost 4.8%

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cases of eye disease related blindness out of 37 Million and it is expected to increase the numbers from 126.6 Million to 191.0 million by 2030(5). The key characteristic of this disease is damaged microvasculature of the retina. Some of the early histopathological changes of this slowly progressing disease include microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, and venous bleeding. But, in more advanced stages, new fragile vessels are formed along the retina and on the posterior surface of the vitreous, and if not treated, they result in the detachment of the retina, leading to blindness (6).

Although hyperglycemia is the major initiator of diabetic retinopathy, hypertension and dyslipidemia are also considered significant risk factors in its development and progression (7,8,9). Despite extensive research in the field to understand the pathogenesis of diabetic retinopathy, the exact mechanism(s) remains elusive making inhibition of the progression of this disease a daunting task. Some of the possible mechanisms implicated in its development include oxidative stress, increased formation of advanced glycation end products, and activation of protein kinase-C, polyol production, and hexosamine pathways (6,10,11). The earliest clinical signs are mainly microaneurysms and intraretinal hemorrhages, and over 95% of patients with 20 years of diabetes and 80% patients with type II diabetes, show these signs (12,6). With the progression of the disease, the number and size of hemorrhages increase and occlusion of precapillary arterioles results in nerve fiber layer infarctions, and cotton wool spots start to appear. Eventually, due to non-perfusion of capillaries, new blood vessels begin to grow, leading to proliferative diabetic retinopathy, and, if left untreated, to retinal detachment (6).

Animal studies have shown that in the early stages of diabetic retinopathy, the basement membrane thickens and capillary cells undergo accelerated apoptosis, resulting in degenerative capillaries and pericyte ghosts (13,14,15). Retinal cells, other than vascular cells, including ganglion cells, also degenerate before vascular cell degeneration (16), and changes in retinal function (electroretinograms and contrast sensitivity) can be seen in patients before any abnormalities in their vasculature (17,18). Another important change that can occur as diabetic retinopathy progresses is diabetic macular edema; the blood-retinal barrier breaks down allowing leakage of plasma from small blood vessels into the macula, resulting in the swelling of the central retina and loss of central vision; these topics are reviewed by experts in the field of diabetic retinopathy (19,20), and are beyond the scope of this article.

II. RELATIONSHIP BETWEEN *BDNF* GENE AND TYPE 2 DIABETIC RETINOPATHY

Brain derived neurotrophic factor (*BDNF*) is a member of the neurotrophic factor family, which plays a key role in regulating survival, growth and maintenance of neurons (21). 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 (22,23). *BDNF* can induce long term potential (LTP), which is considered to be the neurophysiological basis for learning and memory (24). It has been suggested that reduction in *BDNF* expression is a pathogenic factor common to Alzheimer disease and major depression (25,26). Fasting glucose levels and diabetes duration were negatively associated with *BDNF*, suggesting that decrease *BDNF* levels in T2DM may be related to higher glucose levels and longer diabetes duration. A recent study showed a significant association between high blood glucose and low plasma *BDNF* in T2DM (27). Moreover, it was found that high levels of glucose, but not of insulin, had a negative influence on the output of *BDNF* from the brain (27). Furthermore, the reduced serum levels of *BDNF* are consistent with that found in the brain of T2DM animal models. For example, severely decreased mRNA and protein expression of *BDNF* was found in the hippocampus or cortex of type 2 diabetic db/db mice and in diabetic rats (28,29). Low levels of *BDNF* may accompany impaired glucose metabolism, and decreased *BDNF* may be a pathogenetic factor involved in T2DM (27,30).

The finding of lower cognitive performance in T2DM patients is concordant with most of the studies evaluating cognitive function in patients with T2DM (31-34). Lower serum *BDNF* levels were correlated with poor cognitive performance in patients with T2DM. This indicates that serum *BDNF* levels were positively correlated with cognitive function in aging healthy adults (35-36). The exact mechanisms for this relationship are unknown. One possible reason is the neuroprotective function of *BDNF*. *BDNF* plays an essential role in regulating synaptic plasticity (37), which is thought to be the cellular mechanism for learning and memory in adult brains (24). Moreover, LTP, including early and late phase LTP, considered as the neurophysiological basis for learning and memory, is evoked by *BDNF* (38,22,24).

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Animal experiments demonstrate that hippocampal LTP is significantly impaired in *BDNF* knockout mice (39), and this impairment can be ameliorated by upregulation of *BDNF*(40) or by treating with recombinant *BDNF* (41).

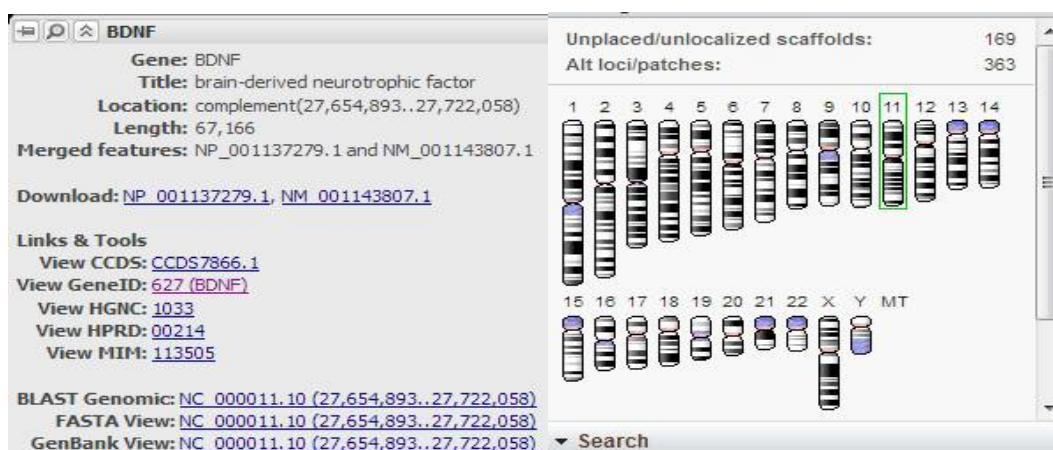


Fig no 2: a) length in base pairs of BDNF gene and b) localization of BDNF on chromosome no 11
<https://www.ncbi.nlm.nih.gov/genome/gdv/browser/?context=gene&acc=627>

III. CHROMATIN REMODELING

The basic subunit of chromatin is the nucleosome, consisting of 146 base pairs of DNA wrapped around an octamer of two copies of each of the core histone proteins H2A, H2B, H3, and H4 (42). The linker histone H1 binds to the DNA between nucleosomes to enable further chromatin compaction. It is through the dynamic reorganization of nucleosomes and higher-order chromatin structure that genetic regulatory elements are made accessible to transcription factors to modify the expression of specific genes (43,44,45). Covalent modifications of DNA and histone proteins disrupt chromatin compaction and also serve as landmarks that are recognized by chromatin-binding proteins that initiate downstream genetic processes. The enzymes that catalyze DNA and histone modification as well as the factors that interact with these marks are collectively termed chromatin remodeling proteins. Mutations in a growing number of these proteins causing developmental and neurodegenerative defects, are evidence of their critical function in the CNS from the embryo right through adulthood. The development of the retina follows defined genetic programs that have been extensively characterized (46,47). An increasing number of studies describe interactions between the transcription factors that control the development of the retina and various chromatin remodeling proteins that may contribute to the execution of critical developmental programs (48). However, much less attention has focused on the epigenetic regulation of retinal neuron maintenance and homeostasis.

IV. HISTONE ACETYLATION

Lysine residues are acetylated at the N terminus of histones and remove positive charges, thereby reducing the affinity between histones and DNA due to which RNA polymerase and transcription factors can easily access the promoter region. Therefore, in most cases, histone acetylation enhances transcription while histone deacetylation represses transcription. Basically acetylation means the introduction of an Acetyl functional group to the Lysine amino acid of the histone tail. And this reaction is carried by Histone acetyltransferases (HATs) and histone deacetylases (HDACs), two enzyme classes that, respectively, catalyze forward and backward reaction kinetics of lysine residue acetylation in specific protein substrates. These substrates most importantly include nucleosomal histones and various transcription factors (TFs), which form part of the transcription initiation complex. Accordingly, HATs and HDACs are found embedded in large multiprotein complexes near euchromatic regions of the chromatin. HATs modify core histone tails

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by post-translational acetylation of specific lysine residues, thereby creating appropriate ‘histone code’ for chromatin modification and enhanced DNA accessibility of TFs. Moreover, TFs like RelA, E2F, p53 and GATA1 are also acetylated by HATs. In addition to enhancing protein stability, by acetylation, in most cases, enhance their transactivation potential by facilitating their interaction with DNA and other proteins of the transcription apparatus. Contrarily, HDACs attenuate transcription process at a particular site by deacetylating these targets. Taken together, the HAT–HDAC system, owing to their involvement in turnover of histone and transcription machinery regulation, is one of the ultimate regulatory switches of gene expression.

In addition to transcriptional regulation, HAT–HDAC system is also postulated to modulate other chromatin-associated processes like replication, site-specific recombination and DNA repair, thereby playing a major role in modulating overall cellular fate. The transfer of an acetyl group to the lysine side chains of histone proteins causes the neutralization of the positive charge on the lysine residues and can therefore disrupt the interactions between histones and DNA within nucleosomes. Acetylation has been described for all of the core histone proteins and is generally associated with chromatin relaxation and transcriptional activation, while deacetylation favors chromatin condensation and transcriptional repression. The extent of post-translational acetylation is determined by the enzymatic activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). It is the net effect of both HAT and HDAC activities that determines the overall acetylation level of histones and impacts the transcriptional status of particular genes. The acetylation of histones has been the most extensively studied chromatin modification in the context of neurodegenerative processes. Despite the different pathophysiologies associated with various neurodegenerative diseases, *in vivo* models demonstrate that a common feature of the degenerative process in the affected neurons is a reduction in the global level of histone acetylation (49). Generally the transcriptional activity is associated with the modified acetylation of histones and this indicates increase transcription machinery to the genes and thus the mechanism activates (50,51).

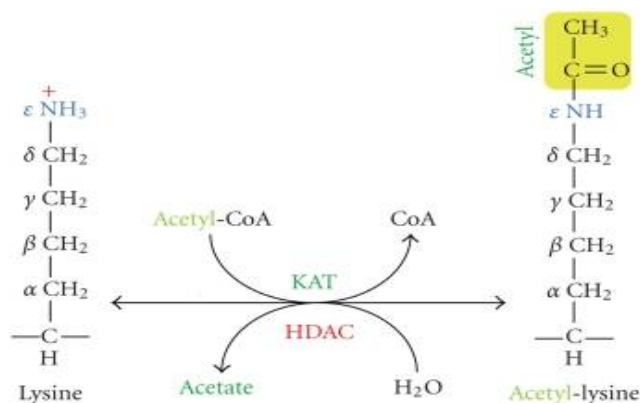


Fig No: 3 Acetylation & Deacetylation on Lysine Residue.

https://www.google.co.in/search?q=acetylation+and+deacetylation+of+lysine+residue&client=firefox-bab&source=lnms&tbm=isch&sa=X&ved=0ahUKEwj3_46yhKnUAhVMtI8KHwYwDUIQ_AUICigB#imgrc=jXVQe9qy1GHS3M:

V. EPIGENETIC MODIFICATIONS ON HISTONES

Within cell nucleus, the fundamental units of chromatin are named nucleosomes. Each nucleosome is formed by 147 DNA base pairs wrapped tightly around an octamer of histone proteins, which is assembled by two copies of each of the four core histones (H2A, H2B, H3 and H4). The DNA between the nucleosomal core particles, and their function is bound by the H1 histone linker, which is used to stabilize the higher order chromatin structures. Central globular

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domain and N-terminal tail is the part of histone proteins which contains multiple sites for potential modifications (52), that include acetylation, methylation, phosphorylation, ubiquitination and sumoylation (53). The principal amino acids that are the feed of these modifications are lysine, arginine, serine, and threonine (54). These type of modifications are responsible for repression or activation of gene transcription depending on the site of the modification, suggesting the existence of a histone code. This hypothesis proposes that specific modifications of histones induce interaction with chromatin associated proteins, producing a differential regulatory response of gene expression (52). These modifications are dynamic in the way that they are actively added and removed by histone-modifying enzymes in a site-specific manner, which is essential for coordinated transcriptional control.

VI. EPIGENETIC MODIFICATION IN DIABETIC RETINOPATHY

Diabetic retinopathy is a multifactorial disease, and this slow progressing disease continues to progress after cessation of hyperglycemia, suggesting that epigenetics could be one of the major contributing factor in its development and progression, but the role of epigenetics in diabetic retinopathy is still in its incipient stages. Diabetic retinopathy, a slowly progressing disease, is associated with a number of metabolic abnormalities (6,55,56). In a cross-sectional study with over 1,000 patients having type 2 diabetes, analysis of their family history suggested a possible genetic and epigenetic basis for the development of diabetic retinopathy (57,58). Experimental evidence using *in vitro* and *in vivo* models of diabetic retinopathy have shown that the activities of HDACs are increased and that of HATs are decreased in the retina and its capillary cells in diabetes, and global acetylation of histones is decreased (59).

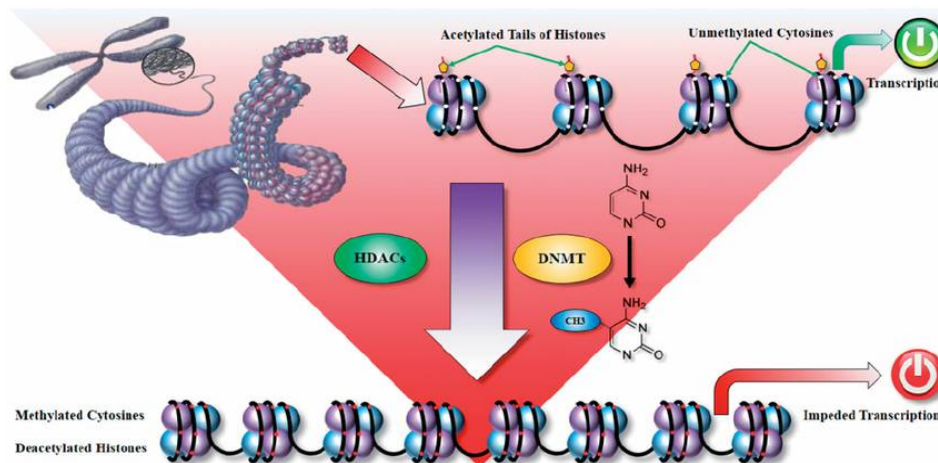


Fig no. 5: Epigenetic alterations through chromatin remodeling.

https://www.researchgate.net/publication/289672966_Epigenetic_Alterations_Underlying_Autoimmune_Diseases/figures?lo=1

VII. THERAPIES TARGETING EPIGENETIC MODIFICATIONS

The translation of gene can be easily altered with the help of epigenetic factors in chronic diseases. As mentioned above, DNA acetylation is one of the most common epigenetic modifications, and Acetylation at specific lysine residue can provide insights into disease diagnosis and prognosis. Thus, Acetylation of genes associated with that disease can be used as a predictor of efficacy for particular drug treatments. Histone modifications can alter gene expression modifying the risk for a disease, and the process is homeostatically balanced by groups of cellular enzymes that add an acetyl group or remove them. Therefore, per available literature the work related to H4 is still in its infancy and this review is mainly focused on H4 Acetylation and Deacetylation of the lysine residue in *BDNF* gene of T2DR. The

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addition and removal of acetyl group from the lysine residue for example (lys5 lys8 lys12 lys16) can help in preventing from the T2DR.

VIII. CONCLUSIONS AND FUTURE DIRECTION:

Histones, as chromatin structure proteins, have recently been discovered & involved in multiple cellular processes and form an important regulatory network by controlling the levels of BDNF in retina. Deciphering such a mechanism represents a step toward unraveling the regulatory network that underlies diabetic complications. This brings us closer to an approach towards personalized medicine for Type 2 Diabetic Retinopathy. Histone (H4) proteins are still in their infancy state and it can help in Diagnosing or treating the Type 2 Diabetic Retinopathy. The results confirmed that by decreasing the rate of apoptosis, BDNF protects retinal neurons from hyperglycemia. However, understanding the structure, modification, and function of histones inside and outside the cells remains challenging. The purpose of this review was to view the role of Acetylation and Deacetylation on *BDNF* gene.

IX. SIGNIFICANCE

H4 protein forms an important regulatory network that control the expression level of *BDNF*, which brings us closer to a prospective therapy for Type 2 Diabetic Retinopathy. Manipulation of H4 protein through acetylation and deacetylation of lysine residue to control *BDNF* expression level in Diabetic retinal endothelial cells may provide a unique and effective “combinational therapy”. Unraveling the relationship between *BDNF* and Type 2 Diabetic retinopathy paves the way to understand disease pathogenesis and how it can be exploited for disease diagnosis and personalized medicine.

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