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Crystal Structure of Tet2 Protein Complex: Regulate Brain-Derived Neurotrophic Factor Insight into Tet-Mediated Oxidation DNA Methylation/De-Methylation Pathway in Different Region In Case Of Type 2 Diabetic Retinopathy

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Abstract: ***Type 2 Diabetic Retinopathy is one of the most common complication of diabetes that affect the blood vessels of the retina, leading to blindness. Interaction between genetic and environmental factors in disease development most likely involves epigenetic modifications. The study so far suggested that epigenetics mechanism (DNA methylation/de-methylation) also play a key role in the pathogenesis of Type 2 Diabetes Retinopathy. DNA methylation protein TET iteratively converts 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) in a Fe (II)/a-ketoglutarate-dependent manner. These studies investigate the substrate binding and catalytic mechanisms of oxidation reactions mediated by TET2 on different substrates through computational approaches. Further structural characterization of docking results shows that TET2 binding efficiency with DNA methylation pathway four different region on the basis of this structure prediction found that step with this highest energy barrier, the energy barriers for the rate determining step order of 5fC>5caC > 5hmC > 5mC, although molecular compound of TET2-α-KG shows higher bind to regulate the TET2 activity. Therefore, based on the result, it was concluded that BDNF-α-KG is a best compound to control the activity of TET2 which control the methylation/de-methylation, normal DNA methylation pathway will control BDNF protein level because of TET down regulation is associated with BDNF gene dysregulation, which is highly important factor to control T2DR. While BDNF and DNA methylation pathway get normalized, it might help in pathogenesis and control of T2DR.***

Keyword- Brain derived neurotrophic factor, molecular compound, Ten-Eleven Translocation protein, Oxidative stress, Retinopathy

I. INTRODUCTION

Type 2 Diabetic Retinopathy (T2DR) is one of the most common complications of diabetes, and is the important cause of blindness in developed countries. After 15 years with diabetes, approximately 80% of patients have retinopathy particularly, the prevalence of type 2 diabetes (T2D) is increasing at an alarming rate [1, 2]. T2DR is a term used for all the abnormalities of the small blood vessels of the retina caused by diabetes. Interaction between genetic and environmental factors in disease development most likely involves epigenetic modifications [3], role of epigenetic mechanisms in the etiology of these disorders and related metabolic abnormalities such as obesity, dyslipidemia, hyperinsulinemia, are often associated with T2D. T2DR has been considered a microvascular disease, but multiple cell types in the retina are affected by T2DR for example, neurons and glial cells [4]. Osmatic procure has been usually regarded as the key factor for the emergence of ocular disease and has been involved in increased vascular permeability, disruption of blood-retinal barrier, microvascular abnormalities, apoptotic loss of retinal capillary cells, involves of microaneurysms, hemorrhages and retinal edema as well as neovascularization in some cases, retinopathy may result in the vision loss.

A. TET mediated DNA methylation and de-methylation

DNA methylation is one of the most studied epigenetic modifications in human cells. DNA methylation and cellular differentiation a tightly timed interplay between DNA methylation, epigenetic regulations including DNA methylation and de-methylation play

critical roles in neural development also plays crucial roles in many biological processes, including regulation of gene expression, maintenance of genomic stability and integrity. Hydroxy-methylation, and active de-methylation regulates gene expression and cellular differentiation in the developing nervous system [5, 6]. DNA methylation is relatively stable compared with most histone modifications, it is a major epigenetic mechanism involving direct chemical modification to the DNA called DNA methylation. Methylation of DNA can change the functional state of regulatory regions, but it does not alter the Watson–Crick base pairing of cytosine. It thus presents the standard 'epigenetic' mark and is functionally involved in many forms of stable epigenetic repression, such as imprinting, and silencing of repetitive DNA [7]. DNA methylation is a "transfer of a methyl group onto the C5 position of the cytosine to form 5-methylcytosine (5mC)", transfer of methyl group with the help of enzyme S-adenyl methionine (SAM) to form 5mC. Changes in DNA methylation patterns play a critical role in development, differentiation and diseases such as multiple sclerosis, schizophrenia, aging, cancer, and diabetes and its complications. DNA methylation is reversible because it does not alter the DNA sequence; however, it is heritable from cell to cell, methylated genes can serve as biomarkers for early detection of disease.

The conversion of 5mC and its oxidized derivatives back to the unmodified state has been proposed to occur by DNA de-methylation can occur either "passive" or "active" de-methylation. "Passive" DNA de-methylation takes place during DNA replication when the newly synthesized strand is not methylated it refers to the failure to maintain DNA methylation patterns across cell divisions and is believed to result in replication-dependent loss of 5mC."Active" DNA de-methylation is independent of DNA replication and refers to an enzymes that process removes or modifies the methyl group from 5mC, although passive DNA de-methylation is generally understood and accepted, the evidence for active DNA de-methylation and how it occurs has been controversial. In part, this controversy has been due to the cacophony of enzymes and pathways implicated in de-methylation. It was reported that TET family proteins play critical roles in DNA de-methylation by converting 5-mC to 5-hmC [8-14]. A key active intermediate, 5-hmC is further processed by several pathways back to unmodified cytosine direct de-methylation of 5-methylcytosine to cytosine does not occur. Instead, all known in vivo conversions of 5mC to cytosine involve replacement of the methylated nucleotide.

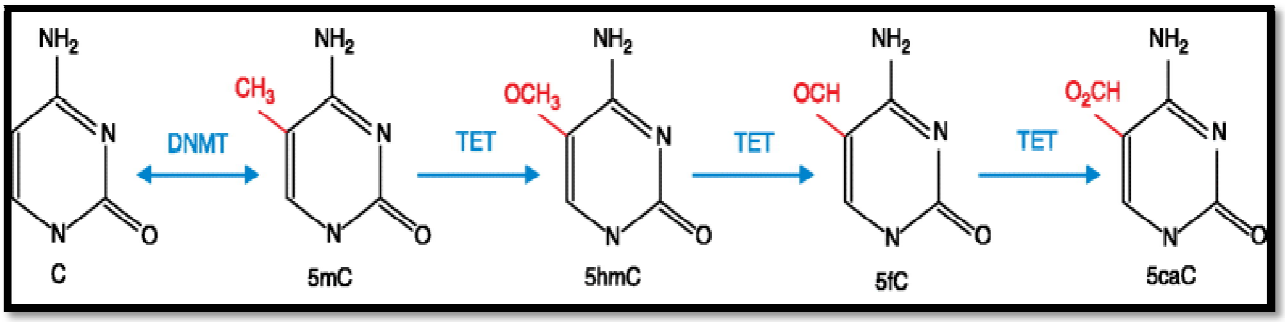


Figure 1; Continuous oxidation of 5mC by TET2 form 5hmC, 5fC and 5caC [15]

Biochemically, irreversible process DNA de-methylation mediated by Ten-eleven translocation (TETs) family of enzyme, TET1, TET2, and TET3 have similar or distinct mechanisms of action, TET2 are more active, bound to ox-mC bases, active site of human TET2 for potential structure–function determinants of stepwise oxidation. In the crystal structures of TET2 bound to DNA, the enzyme is truncated to the minimal regions necessary for catalytic activity [16]. TET protein convert 5mC into 5hmC, 5-formylcytosine, and 5-carboxylcytosine in a stepwise manner [17, 18], previous biochemical studies revealed that TET proteins are more active on 5mC than on 5hmC and 5fC. TET2 is primarily responsible for modulating 5hmC dynamics. 5hmC, 5fC and 5caC are chemically distinct modifications of C that could be specifically recognized by different DNA-binding proteins. The oxidized 5-substituents also have different steric and electronic properties, which can promote alternative nucleobase tautomers or, in the case of 5fC and 5caC, destabilize the N-glycosidic bond[19, 20]. Depletion of TET2 leads to increased proliferation and reduced differentiation *in-vitro* and *in-vivo*. Genome-wide transcriptional analyses reveal important epigenetic roles of TET2 in maintaining the transcriptome landscape related to neurogenesis.

B. Brain-Derived Neurotrophic Factor (Bdnf)

Brain-derived neurotrophic factor is a neurotrophin, it has a role in proliferation, differentiation, survival, and death of neuronal and non-neuronal cells [21]. Methylation status of the BDNF gene is associated with fear learning, memory, and stressful social

interactions. It has been suggested that DNA methylation may play a role in regulation of the BDNF gene in the path physiology of T2DR and DNA methylation and de-methylation may be used as targets for T2DR therapy.

C. Impact Of Dna Methylation On Bdnf Expression

DNA methylation is a fundamental epigenetic mechanism for gene silencing throughout lifecycles [22]. Neuronal activity induces dynamic DNA methylation changes in the BDNF gene region. The BDNF gene is regulated by neural activity in a temporal and spatial manner study prove that DNA methylation negatively regulate the expression of BDNF. Emerging evidence suggests that elevated BDNF exon IV DNA methylation is a mechanism for BDNF down-regulation in adverse environmental conditions. It may be suggest that methylation level increases in diabetic retina known through DNA de-methylation, De novo DNA methylation together with DNA de-methylation are predominantly thought to be implicated in neuronal plasticity [23].

TET2 is a main enzyme of DNA methylation/de-methylation pathway (formation of downstream derivative), previous *in-vitro* study shows that TET-DNA complex binding affinity thus, in this study to check the hypothesis that over expression of TET2, may lead to down regulate, its target genes such as BDNF which will contribute to the pathogenesis of T2DR through the computational approach.

II. METHODOLOGY AND COMPUTATIONAL DETAILS

A. Model Construction And Preparation

The crystal structures of TET2–5mC–DNA (PDB: 5D9Y), TET2– 5hmC–DNA (PDB: 5D9Y), TET2–5fC–DNA (PDB: 5D9Y), TET2– 5caC–DNA (PDB: 5D9Y), and the molecular compound of TET2 protein TET2,- 2-HG-DNA (PDB: 5D9Y) and TET2- α-KG (PDB: 5D9Y) were used as initial coordinates to build the pre-catalytic TET2–5mC, TET2–5hmC, TET2–5fC and TET2-5caC models. Crystal structure was built molecular compound of TET2, 2-hydroxyglutarate and α-ketoglutarate and 5mC, 5hmC, 5fC and 5caC and by using protocol of pymol software (https://pymol.org).

B. Molecular Dynamics Simulation Setup

Auto Dock Vina is one of the apt and reliable software available for drug discovery, molecular docking and virtual screening offering multi-core capability, high performance, enhanced accuracy and ease of use. Auto Dock Vina significantly improves the accuracy of the binding mode predictions Additionally, Auto Dock. Three key steps are involved in the docking simulations:

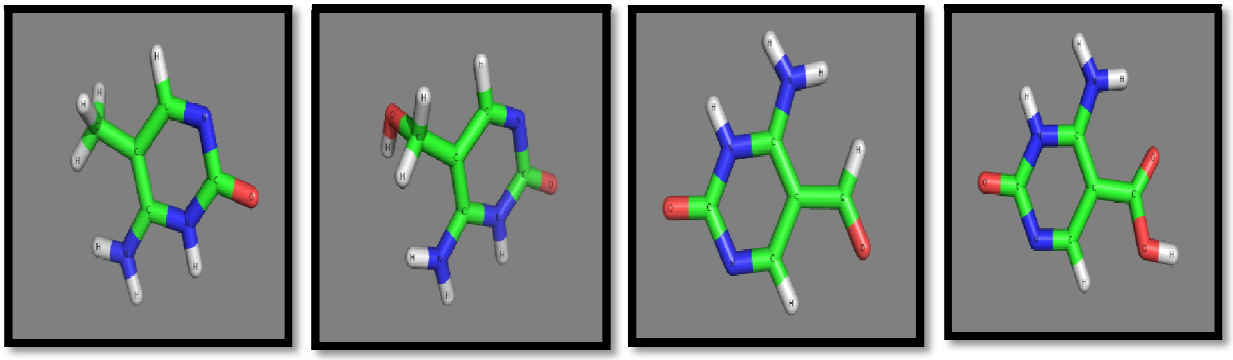
1) Preparation of protein (rigid and flexible)
2) Defining the active site (Grid)
3) Ligand preparation

Molecular docking of TET2–5mC–DNA (PDB: 5D9Y), TET2– 5hmC–DNA (PDB: 5D9Y), TET2–5fC–DNA (PDB: 5D9Y), TET2– 5caC–DNA (PDB: 5D9Y), and the molecular compound of TET2 protein TET2-2-HG-DNA (PDB: 5D9Y) and TET2-α-KG (PDB: 5D9Y) by using protocol Auto Dock Vina (http://autodock.scripps.edu/resources/adt). AutoDock has applications in: X-ray crystallography, structure-based drug design, lead optimization, virtual screening (HTS), combinatorial library design, protein-protein docking, chemical mechanism studies, docking results in PDBQT format, automatically read into view Dock [24].Vina uses the PDBQT molecular structure file format used by Auto Dock. PDBQT files can be generated (interactively or in batch mode) and viewed using MGL Tools. Other files, such as the Auto Dock and autogrid parameter files (GPF, DPF) and grid map files are not used.

Protein-protein interaction of BDNF protein and modified protein TET2 BDNF-2HG (PDB:1B8M) and BDNF- α-KG (PDB: 1B8M) by using protocol Hex server (http://hexserver.loria.fr).

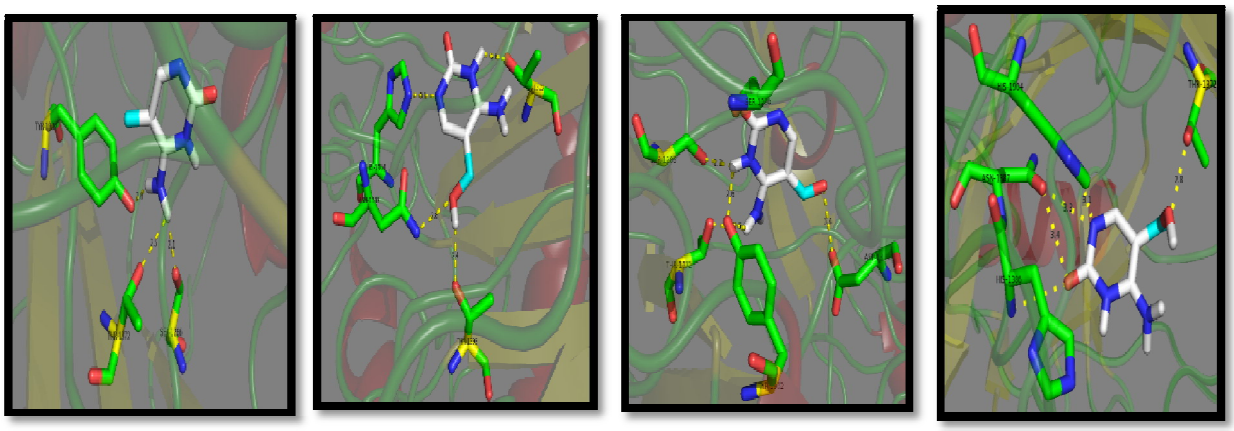
Center: [x] [y] [z] - Box center in the receptor coordinate system; can be edited directly.
Size: [x] [y] [z] - Box dimensions along X, Y, and Z in the receptor coordinate system can be edited directly.

(a) (b) (c) (d)



5-methylcytosine5-hydroxymethylcytosine5-formylcytosine5-carboxylcytosine

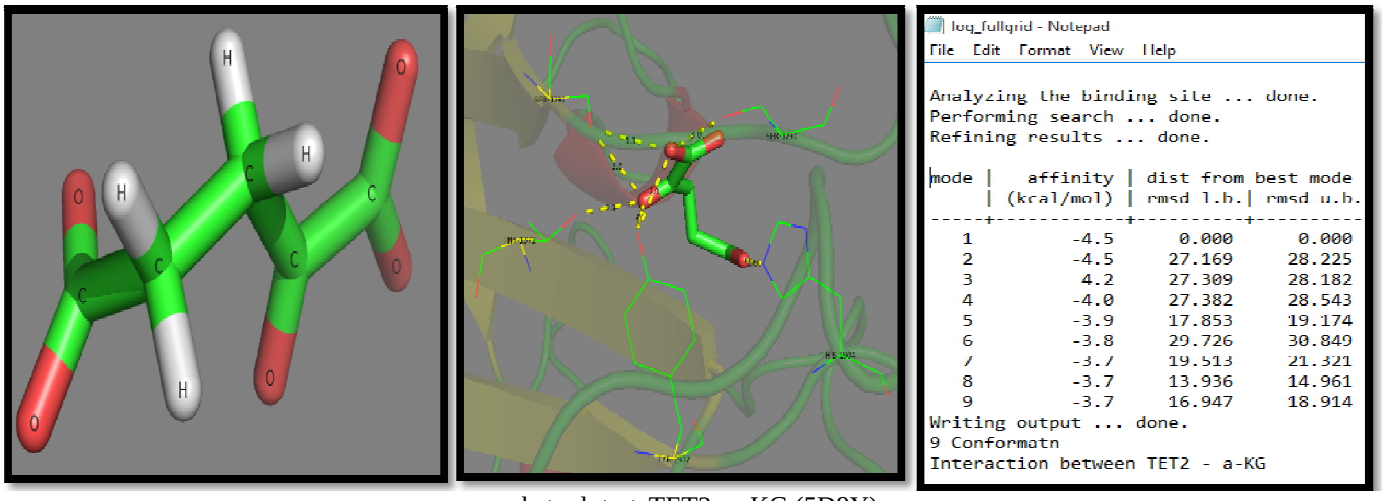
(a) (b) (c) (d)



TET2–5mC (5d9y) TET2–5hmC (5d9y) TET2–5fC (5d9y) TET2-caC (5d9y)

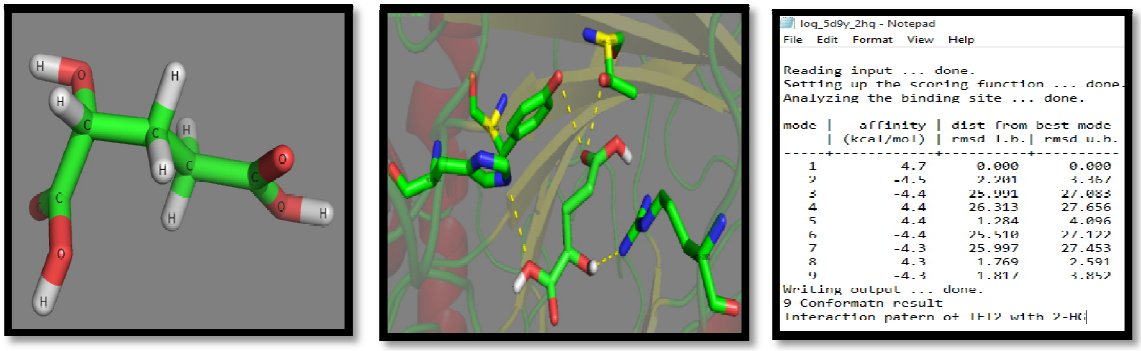
Figure 2; Crystal structures of 5mC, 5hmC, 5fC and caC built using by pymol and interaction pattern of TET2 (5D9Y) protein with different region of DNA methylation pathway (5mC, 5hmC, 5fC and caC) to check the binding efficiency and interaction pattern of TET2 protein. Interaction of TET2–5mC–DNA (PDB:5d9y), TET2–5hmC–DNA (PDB:5d9y), TET2–5fC–DNA (PDB:5d9y) and TET2-caC-DNA (PDB:5d9y) using by Auto dock Vina. The equilibrated active site conformant of each complex model. The hydrogen bonds are shown as dashed lines in yellow colour (distance b/w 0-2 A^0)

(e)



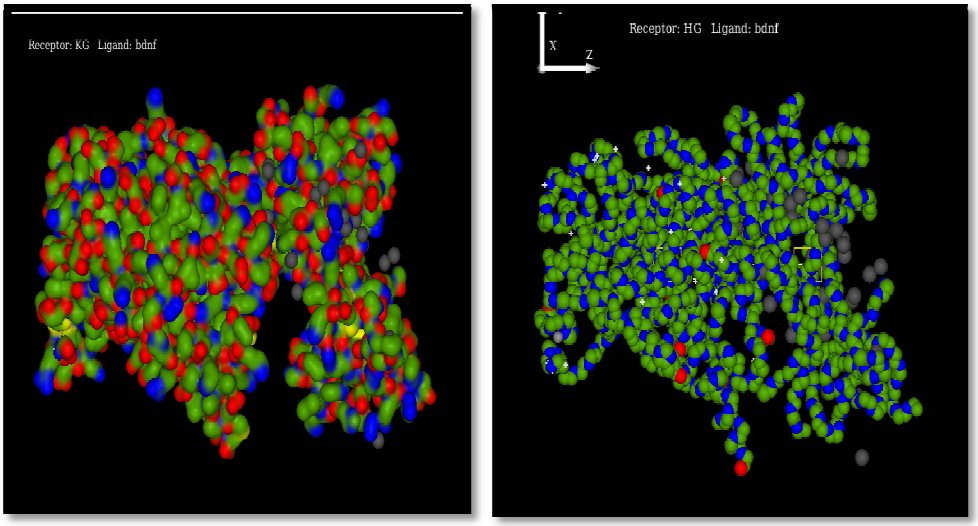
α-ketoglutrateTET2- α-KG (5D9Y)

(f)



2-hydroxyglutrateTET2-2-HG (5D9Y)

Figure 3; Crystal structures of TET2 protein molecular compound α-ketoglutrate and 2-hydroxyglutrate that regulate the activity of TET2 protein, crystal structure built using by pymol and interaction of TET2 (PDB:5D9Y) and it's molecular compound α-KG and 2-HG, TET2-α-KG(PDB:5d9y), TET2–2HG (PDB:5d9y) to check the interaction pattern and binding efficiency of protein with molecular compound. The equilibrated active site conformant of each complex model. The hydrogen bonds are shown as dashed lines in yellow colour (distance b/w 0-2 A^0).



Interaction BDNF-α-KG (1B8M)Interaction BDNF-2-HG (1B8M)

Figure 4; Modified protein further docked with BDNF protein by using HEX server of protein-protein interaction modified protein α-KG and 2-HG docked with BDNF (PDB: 1B8M) to check the interaction pattern of BDNF protein with modified proteins.

TET2 protein was too large for the frequency analysis, so truncated the system to an area containing all amino acids with at least one atom within a 15 Å radius of the iron center structure prediction of Auto dock Vina docking results on the basis of different parameters TM-c score, RMSD value, binding affinity (kcl/mol). Auto dock shows 9^{th}conformantresult 1^{st} and 2^{nd} values are considered best in case of standard result, if not found in 1^{st}conformant then other conformant was selected, other 9^{th}conformantjust a references. Conformant stability of TET2–5mC (5d9y) complexes during MD simulations. Evolution of RMSD values of protein backbone atoms catalytic sites were obtained by performing vibrational frequency calculations.

III. RESULTS AND DISCUSSION

A. Modelling And Molecular Docking Simulations Of The Tet2–Substrate Complexes

Auto Dock Vina software used to drug discovery, molecular docking; crystal structures of TET2 protein interact with different region of methylation pathway, interaction pattern of different region of methylation and TET2 (5D9Y) protein, TET2–5mC, TET2–5hmC, TET2–5fC and TET2-caC models. Conformant stability of TET2–5hmC (5d9y) complexes protein backbone atoms catalytic sites (HIS-1904, ANS-1387, THR-1393, TRY-1372). Conformant stability of TET2–5fC (5d9y) complexes protein backbone atoms catalytic sites (SER-1290, 1286, THR-1372, TYR-1902, ASP-1307). Conformant stability of TET2–5caC (5d9y) complexes protein

backbone atoms catalytic sites (HIS-1904, ANS-1387, HIS-1386, THR-1372). The low average RMSD value (less than 2 Å) indicated that both protein (5d9y) and DNA (5mC, 5hmC, 5fC and 5caC) remained stable in each model. 1st conformant of docking TET2–5mC, TET2–5hmC, TET2–5fC and TET2-caC shows that different binding affinity and RMSD values 5d9y-mC binding affinity was -4.8, 5d9y-hmC binding affinity was -4.8, 5d9y-fC affinity was -5.5 similar to TET2–5mC and 5d9y-caC affinity was -5.1 docking complex s.no. 1st and 3rd have lowest binding affinity on the basis of this result interpret 5d9y-fC complex shows that best binding affinity of TET2 protein, it highly regulate the TET2 protein in the process of DNA de-methylation.

Table 1. Autodock Vina result TET2 (5d9y) bind to DNA methylation in different region

S.No	Molecule	Binding Affinity (kcl/mol)
1	5d9y-mC	-4.8
2	5d9y-hmC	-4.8
3	5d9y-fC	-5.5
4	5d9y-caC	-5.1

Modelling and molecular docking of TET2 and its molecular compound α-KG and 2-HG, conformant stability of TET2–2HG (5d9y) complexes during MD simulations. Evolution of RMSD values of protein backbone atoms catalytic sites (HIS-1904, THR-1372, ARG-1261) atoms and modified nucleotide 5mC atom. Conformant stability of TET2–*α*-KG (5d9y) complexes protein backbone atoms catalytic sites (SER-1206, 1290, HIS-1204, TYR-1902, THR-1372). molecular compound have an active site for binding of particular enzyme binding pocket, docking of TET2-2HG (5d9y), binding affinity -4.5 and TET2-*α*-KG (5d9y) binding affinity -4.7, *α*-KG shows that highest binding affinity as compare to 2-HG molecules that is -4.5 result shows that *α*-KG > 2HG. The predicted binding ligands and ligand-binding residues are highlighted in yellow-blue domains respectively.

Table 2. Autodock Vina result TET2 (5d9y) and their molecular compound binding affinity

S.No	Molecule	Binding Affinity (kcl/mol)
1	TET2-2HG	-4.5
2	TET2- α-KG	-4.7

RMSD value root-mean-square deviation of atomic positions RMSD is the measure of the average distance between the atoms (usually the backbone atoms) of superimposed proteins. The low average RMSD value (less than 2 Å) indicated that both protein and DNA remained stable in each model. Found that TET2-α-KG (5d9y) have a higher binding affinity of TET2 protein and molecular compound α-KG shows that binding of TET2 complex. According to results obtained, it was predicted that 5d9y-α-KG have best result, α-KG molecule regulate the activity and functions of TET2 enzyme. TET2 bind to fC region with higher binding affinity so molecular compound of TET2- α-KG primary bind to fC region of methylation pathway and regulate the process, TET2 protein regulate the BDNF gene that modified proteins further docked with BDNF (1B8M) protein and structure predict that *α*-KG shows higher binding affinity with BDNF gene to regulate the TET2 activity to control the methylation/de-methylation process. At last, from the results obtained, it was concluded that α-Ketoglutarate is the best molecular compound which gets bind to BDNF protein with higher affinity to control the whole process/pathway of BDNF, which is very crucial for normal functioning to prevent T2DR. Thus, binding of this molecule with BDNF may help in controlling T2DR.

IV. CONCLUSIONS

In this study, we thoroughly investigated TET2 mediated oxidation on its substrates—5mC, 5hmC, 5fC and 5caC—in order to characterize the source of the substrate preference of TET2 (5D9Y). Molecular docking (MD) simulations and ‘‘Alchemical’’ free energy calculations were performed based on the four TET2– substrate complex structures and the results indicated that 5mC, 5hmC, 5fC and 5caC could all stably bind to the active site of TET2 with similar binding free energies, which is in accordance with previous biochemical experimental reports that TET2 binds to 5mC, 5hmC, 5fC and 5caC containing DNA with comparable binding affinities. Subsequently molecular docking substrate predict that TET2 protein highly bind to 5fC region of DNA methylation pathway on the basis of this structure prediction found that step with this highest energy barrier, the energy barriers for the rate determining step still follows the order of 5fC >5caC > 5hmC > 5mC. Molecular compound of TET2-α-KG primary bind to 5fC complex of methylation pathway and then other substrates, activity of the TET2 protein molecular compound α-KG regulate the

TET2 activity and spontaneously affect the DNA methylation/de-methylation pathway on 5fC region primary and then other regions of methylation pathway. Furthermore molecular docking simulations modified proteins that shows the higher affinity with BDNF protein that BDNF protein regulate the TET2 activity. In summary, our computational studies suggest that the difference in the energy barriers of the hydrogen abstraction reaction step during the whole catalytic cycle of TET2 mediated oxidation contributes to the substrate preference of TET2. As TET proteins are highly conserved in the catalytic site, the substrate preference is potentially an intrinsic feature of TET proteins. Therefore, based on the result, it was concluded that BDNF-α-KG is a best compound to control the activity of TET2 which control the methylation/de-methylation, normal DNA methylation pathway will control BDNF protein level because of TET down regulation is associated with BDNF gene dysregulation, which is highly important factor to control T2DR, when BDNF and DNA methylation pathway get normalized, it might help in pathogenesis and control of T2DR. Conversely, a small molecule interacting with a protein can be modified in order to change its affinity and its biological activity to obtain new molecular probes or drugs.

V. ACKNOWLEDGEMENTS

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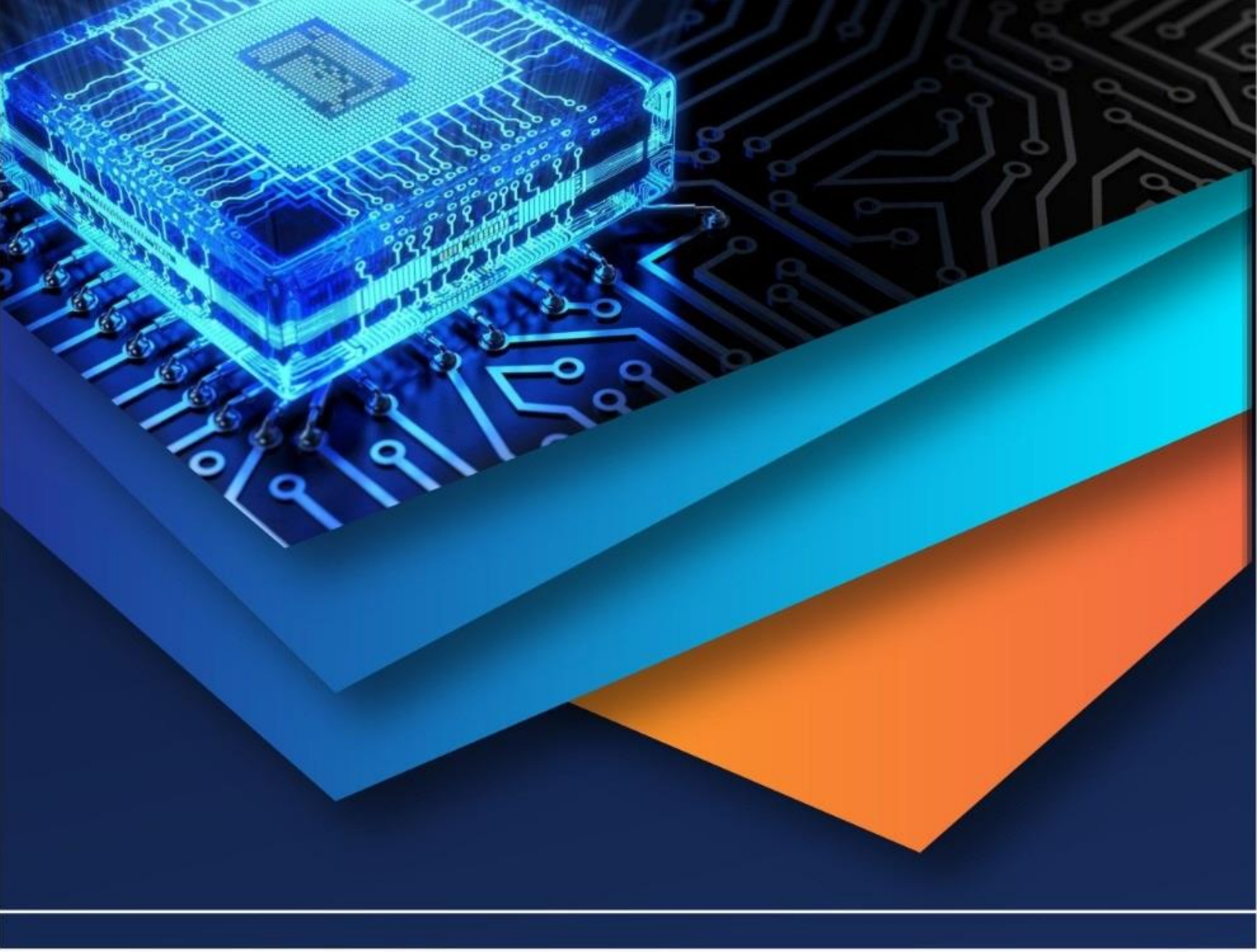

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