Docking Studies between the Predicted Model of Mouse Zinc Finger MYND Domain-Containing Protein 19 and Cofactor Product AdoHcy; towards Drugs Development against Cancer, Obesity and Cardiovascular Diseases

Bertin Mugabo¹, Rene Iradukunda¹, Jeanne Marie Gatanganwa¹, Jean Chrisostome Ufitinema¹ and Dieudonne Mutanga¹*

¹University of Rwanda, College of science and Technology, Department of Biology, P.O. Box 3900 Kigali-Rwanda

*Corresponding Author: d.mutangana@ur.ac.rw, mature02@gmail.com

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Abstract

Mouse Zinc finger domain-containing protein19 (ZMYND19) is a zinc-finger protein questioned after recently published data reported its C-terminal domain of 49 residues to be associated with cancer, obesity and cardiovascular diseases. The potent drugs are suggested to come from its interactions with ligands understanding. However, the diseases are becoming worse because the three-dimensional structure of Mouse ZMYND19 is not yet reported. Thus, this study analyzed structural interactions between the predicted 3D structure and cofactor products S-Adenosyl homocysteine (AdoHcy) using the computational approaches. Pairwise sequence alignment was performed in the iterated mode of protein blast against protein data bank (PDB) and CLUSTAL omega server was used to perform multiple sequence alignment. Phylogenetic analysis was performed using the PHYLIP package. Structure prediction was successfully completed with the use of SWISS model by exploring homology modeling. The predicted Model structure was evaluated using both ERRAT and PROCHECK servers. Docking studies were performed with the HEX8 package. The evaluation results of the predicted 3D structure suggest that the model is of good quality. Docking studies revealed a high affinity (−214.24 KJmol⁻¹) between the predicted 3D model and AdoHcy ligand. The interaction between the bound molecules suggests both compounds to be good candidates for cancer, obesity, cardiovascular diseases, thus these two compounds could be considered at the frontline for a potent drug development.

Keywords: ZMYND19, AdoHcy, docking, cancer, cardiovascular diseases
1. Introduction

Mouse Zinc finger (myeloid translocation protein 8, Nervy, Deaf1) (MYND) domain-containing protein19 (ZMYND19) is a zinc-finger protein that interacts with Melanin-concentrating hormone receptor1 (MCH-R1). This protein has 227 residues, mainly characterized by a C-terminal MYND domain with 49 amino acids. The MYND domain is predicted to be involved in protein-protein interactions, mainly in gene expression (Francke et al., 2005). Interest in Mouse MYND19 has grown because of the recent report of Jiang (Du et al., 2014) indicating that probably it is involved in the control of cell regeneration, where its defects are associated with cancer. Again, Mouse ZMYND19 is questioned for its specific interaction with the C-terminus of Melanin-concentrating hormone receptor1 (MCH-R1), a protein that balances body energy-food intake utilization. The overexpression of (MCH) leads to utilization of less energy than food intake (Högberg et al., 2012) and causes obesity and eventually cardiovascular diseases.

In light of these protein interactions, there is a suggestion that Mouse ZMYND19 may be involved as a regulatory molecule in MCH-R1 signaling (Ba & Richter, 2002). Despite all these findings, cancer, obesity, cardiovascular diseases are becoming pandemic due to the lack of appropriate understanding of the ZMYND19 protein and its three-dimensional (3D) structure. Thus, as a consequence, Mouse ZMYND19 –biomolecules interactions cannot be understood (Schatz, 1997). The ligand proposed for docking with Mouse ZMYND19 (3D) structure is a peptide S-Adenosylhomocysteine (AdoHcy). There are many different reasons to use this ligand. First, AdoHcy is a strong feedback inhibitor of all S-adenosylmethionine (AdoMet) dependent methylation reactions (Francke et al., 2005). Second, methylation is vital for gene activation and deactivation, where defects in methylation of genes responsible for cell growth in general cause cancer (Witvrouw et al., 1997); recall that Mouse ZMYND19 protein is suspected to control signals in the cell cycle (Ba & Richter, 2002). Therefore, combining this information it has been suggested that probably methylation reactions may be controlled by regulating intracellular concentrations of AdoHcy (Wu et al., 2006). To date, there is no report talking about AdoHcy and Mouse ZMYND19 interaction, but probably if both can interact; this can be a good starting point for designing inhibitors of Mouse ZMYND19 for treating cancer, cardiovascular diseases, and obesity. Therefore, the objective of this study is to predict Mouse ZMYND19 (Q9CQG3: UniProt ID)
3D structure and eventually to predict structural interactions between the 3D structure of Mouse ZMYND19 and cofactor products AdoHcy under a computational approach.

2. Material and Methods

2.1. Three dimensions (3D) structure prediction of Mouse ZMYND19 and Docking with AdoHcy.

The process was started with pairwise alignment which was performed using (Q9CQG3: UniProt ID) (Wu et al., 2006). Homologous sequences were retrieved using an iterated mode of psi-blast against PDB (Berman et al., 2000). And then, multiple sequence alignment (MSA) was run using CLUSTAL/Omega (Sievers & Higgins, 2014) server along with its phylip format (Jordan, 2017) activated in order to assess sequence homology and conserved residues among the sequences retrieved. To carry out phylogenetic analysis phylip-3.695 package (Bordoli et al., 1994) was used aiming to verify if the identities shown by alignment results were due to ancestral-relationship. Then 3D structure prediction was performed under SWISS model/homology modeling server (Schwede, 2003), this method uses previously predicted structures as a pattern. After minimizing the energy of the built model with SWISS PDB Viewer (Peitsch, 1997), the structural assessment was done to assess the quality of the model built. The stereochemistry and non-bonded atomic interactions were checked by PROCHECK (Laskowski, 1993) and ERRAT (Andras Fiser, 2014), respectively.

2.2. Docking of the predicted three dimensions (3D) model of Mouse ZMYND19 onto AdoHcy ligand.

Docking study between AdoHcy (ligand) and the predicted 3D of Mouse ZMYND19 (receptor) was performed under HEX8 software which uses Spherical Polar Fourier Correlations approach (Ritchie & Kemp, 2000). The ligand along with the receptor was loaded into HEX8, then docking was started by selecting the docking, electrostatic and shape options of the package. After docking the total binding energy (E-total) was recorded and the complex was brought to SPDB viewer (Peitsch, 1997) to display the interacting residues within 5 Å and hydrophobic patches.

3. RESULTS AND DISCUSSION

3.1. Pairwise alignment.

The results reported by PSI BLAST algorithm indicate homologous protein retrieved from PDB. 28 hits that have similarities, having the E-value greater than the threshold, are reported in figure 1.
FIGURE 1 List of homologous protein with significant alignments to query sequence on iteration 21 retrieved by PSI-BLAST

The graphical overview (Figure not shown) indicates that no red or pink bar reported which would indicate most and moderate related respectively; the presence of green and black bars indicates more distantly related and unrelated proteins to Mouse ZMYND19 respectively. Since the green bars over dominate black bars, this reflects that many BLASTP sequences aligned are more distantly related to Mouse ZMYND19. Fortunately, the Figure 1 illustrating the list of BLASTP hits with smaller expected values (e-value) support graphical overview results; since it confirms some subject’s identity over than 30% indicating that it is within the safe zone. Combining these results and recommendations made by Grzegorz (Boratyn et al., 2012), there is a suggestion that the resulting alignment similarities from the database search are not caused by random chance.

3.2. Multiple Sequence Alignment.

Multiple sequence alignment revealed the residues which are conserved with the query sequence with the top five subjects. The asterisk (*) indicates positions which have a single but fully conserved residues in all sequences. The colon (:) indicates conserved residues between proteins of strongly similar properties. The period (.) indicates conserved residues in almost all aligned proteins with weakly similar properties (Figure 2).
These results solidify the Pairwise alignment results because Mouse ZMYND19 residues “Cys\textsuperscript{1}, 11, 24, 27, 33, 37, 49, Gln\textsuperscript{25, 38}, Try\textsuperscript{4}, Arg\textsuperscript{26}, Trp\textsuperscript{42}, Pro\textsuperscript{43}, His\textsuperscript{45}, and Lys\textsuperscript{46}” are full conserved in 3QWV, 4YND, 3RIB, 4WUY, 3TG4 sequences. Among these conserved residues, the more numbers of cysteine and presence of histidine (His\textsuperscript{45}) in Mouse ZMYND19 reflect their function. In fact, it is cysteine and histidine residues which bind zinc in zinc finger domains, and then these domains fold into a 3D structure. Once folded, these domains become functional and recognize specific nucleotides, or protein targets. In the absence of zinc or when cysteine or histidine are interrupted, these domains are unfolded and cannot function as explained in the study conducted on function of cysteine and histidine in zinc finger proteins (Michalek et al., 2011).

3.3. Phylogenetic analysis.

The \textit{Phylip} package has successfully built a phylogenetic tree. Among 100 trees generated, one consensus tree was selected for more analysis. Branches in the consensus tree illustrates families of proteins. The numbers shown on the branches indicate the number of times the partition of the species appeared into the two sets which are separated by that branch occurred among the trees out of 100 trees (Figure 3).
FIGURE 3 Consensus tree showing the relationship of top 15 homologous proteins to the query protein (Q9CQG3), the tree was build using Phylip package

In a phylogenetic tree; the branches split as proteins diverge, then each protein occupies a position according to its constituents, where protein sharing many constituents occupy closet branches (Edwards et al., 1967). The consensus tree shows two main separate families of proteins and one protein out the families. Unexpectedly in the consensus tree, the first eight proteins (3QWV_A, 4YND_A, 3RIB_A, 4WUY_A, 3TG4_A, 5ARF_A, 3S7B_A, 5KJK_A) reported by BLASTP as matching proteins, diverge in one branch away from protein (Q9CQG3) suggesting that this family is very distantly related to (Q9CQG3) (Boratyn et al., 2012). Again the ninth (3N71) hit of BLASTP is out the group in the tree, suggesting that it is evolutionarily unrelated to all remaining proteins according to similar study done on snake venom protein (Hombalimath & Shet, 2012). On the other hand, all the proteins at the second branch (3OXG_A, 5EX3_A, 5CCL_A, 5HI7_A, 3RU0_A, 3QWP_A) share a single ancestral with protein in question (Q9CQG3), however after a long time they diverged in different branches, the proteins share an evolutionary relationship with the query. With respect to alignment results, 5EX3-A shows more relationship than all other proteins analyzed to query (Q9CQG3). In fact, 5EX3-A was detected to be on top of all homologous proteins retrieved by BLAST, represented by the green bar and $3^{-13}$ e-value. Considering this and consensus tree that shows both (Q9CQG3) and 5EX3-A to be in the same family and in the closest branches than other proteins, both proteins are suggested to be more or less evolutionary
related than others on the consensus tree. As it is recommended by Fiser (András Fiser, 2004), this closest relationship and the safe zone identity (38%) between 5EX3-A and target protein was considered.

3.4. Three-dimensional structure predictions and model evaluation

The model of the query protein was successfully predicted (Figure 4 (a)) through homology modelling techniques using the crystal structure of Histone Lysine Methyltransferase SMYD2 (ID: 3QWV_A) from house mouse, as a template structure (Figure 4 (b)) to predict model Mouse ZMYND19. The template structure revealed several secondary structural information including 11 beta sheets, 17 alpha helices and 28 turns. It contains 3 zins labeled ZN501, ZN502 and ZN503 (Figure 4 (b)).

![Figure 4](image1.png)  
(a) Predicted 3D model structure of Mouse ZMYND19 and (b) aligning region of X-ray structure of SMYD2 (Histone Lysine Methyltransferase SMYD2 (ID: 3QWV_A) used as template through homology modelling. Images were produced via chimera package. The position of two zinc elements is labelled in black.

PROCHECK web portal was used to evaluate the stereochemistry of the energy minimized predicted model (-3795.33 KJmol\(^{-1}\)) as illustrated in figure 5. Stereochemistry quality evaluated with PROCHECK (Figure 5) shows that 89.5% residues are in the core region, 10.5% residues are found in the allowed region, whereas nothing is found in general nor in the non-allowed regions. And the overall G-factor is below zero (-0.04).
FIGURE 5 PROCHECK summary illustrating the distribution of all residues of the predicted model in the Ramachandran plot

These results prove the predicted 3D structure to be good since they are not far from what Duda (Duda, 2003) has found using PROCHECK to determine a structure of carbonic anhydrase where he finds 88.4% residues in a core, the rest are in the allowed region.

Non-bonded atoms evaluated with ERRAT (Figure 6) reported 80.556% overall quality factor, after loop refinement using ModLoop server (Fiser & Sali, 2003). Since the normally accepted range for a high-quality model is >50 overall quality factor (Gundampati, 2012);

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**FIGURE 6** ERRAT output showing the overall quality factor of the predicted model of Mouse ZMYND19. On the error axis, two lines show the confidence with which it is possible to reject regions that surpass the error value. Therefore, the above results suggest the predicted model to be good and prompt this study to further analysis with docking study.

Figure 7 as displayed by chimera package (Pettersen et al., 2004), illustrates the superimposition of secondary structural information between the query and the template structure of the protein used for homology modelling of the query sequence with an overall RMSD of 0.202 Å.

**FIGURE 7** structural superimposition between the query and the Crystal Structure of mouse SMYD2 (3QWV_A) used as template for building the model structure of the query (Overall RMSD: 0.202 Å). The image was generated using chimera package (Pettersen et al., 2004)
This superimposition indicates that almost the entire length of the 3D structure predicted model is conserved in the template structure. This is not far from the report of Hombalimath (Hombalimath & Shet, 2012) who states that often protein structures are more conserved than their sequences. In a research conducted by Kashyap and his colleagues (Kashyap et al., 2011), similar kinds of tools were used for validating the 3D structure of Cry1Ab17 from Bacillus thuringiensis predicted using X-ray structure of Cry1Aa1 from Bacillus thuringiensis.

3.5. Docking studies between mouse ZMYND19 and AdoHcy ligand

The report given by HEX 8 package after docking AdoHcy and the predicted 3D model of Mouse ZMYND19 delivered -214.24kj/mol (e-total). Eleven residues were involved in the interaction with the ligand as displayed by DeepView software. These interacting residues are: Cys$_6$, His$_{7, 45, 48}$, Try$_{8, 32}$, Pro$_9$, Ala$_{30, 44}$, Arg$_{31}$ and Asp$_{41}$ (Figure 8).

![Figure 8](https://dx.doi.org/10.4314/rijeste.v4i1.3)

**FIGURE** 8 Interacting residues between the predicted model of Mouse ZMYND19 and AdoHcy ligand. Docking was done using the Hex 8 package and the image was displayed under SPDB viewer. The yellow color indicates AdoHcy, while the rest are interacting residues from the protein.

Docking between Mouse ZMYND19-AdoHcy and MSA results, both have shown a correlation between them. Among these interacting residues, amino acids Try$_{32}$, Asp$_{41}$, and His$_{45}$ are significant because they are also fully conserved in the top five proteins used in the MSA. Recall that His$_{45}$ recognizes and binds to zinc in zinc finger proteins to assure protein folding (Michalek et al., 2011). Unfortunately, there is no
literature talking about Try$^{32}$, Asp$^{41}$. In addition, free binding energy revealed by docking study was satisfactory since they showed highest negative binding energies (-214.24kJmol$^{-1}$), suggesting these interactions to be natural. This shows that AdoHcy binds strongly to the target protein; since the more, the negative energy is the strong binding (Heifetz & Katchalski-katzir, 2002).

3.6. Hydrophobic patches of mouse ZMYND19- AdoHcy complex

The DeepView package was successfully used to display hydrophobic patches. Residues that form six hydrophobic patches within 3D structure of Mouse ZMYND19, complexed with AdoHcy, were detected. The window "Surface and Cavities" list the patches sorted by their respective area; the area 2480 Å marked by black color is the hydrophilic surface of the protein, and it is hidden by default. Patch with area 67 Å marked by red color cover Try$^{42}$, Lys$^{47}$ and His$^{45}$ which is one of the interacting residues. The remaining four patches are marked by white color. The patch with area 56Å covers Pro$^{10}$, Val$^{13}$ residues; patch with area 55Å covers Ile$^{14}$, Glu$^{15}$, Leu$^{18}$, Cys$^{33}$ residues; patch with area 41Å covers Cys$^{27}$, Val$^{29}$ residues; patch with area 39Å covers Val$^{13}$, Ile$^{14}$, Gln$^{36}$ residues and patch with 36Å area covers Trp$^{42}$, Pro$^{43}$, Lys$^{46}$ residues (Figure 9).
FIGURE 9 Residues of Mouse ZMYND19-AdoHcy complex that form hydrophobic patches under SPDB Viewer. AdoHcy is marked by yellow color.

Hydrophobic patches detection is among techniques used to check whether a ligand binds to the regions of the target protein. In this study, residues covered by these patches were detected using SPDB Viewer. Interestingly, among six hydrophobic patches that were found, there is a patch covering His45, an interacting residue with AdoHcy and fully conserved in the top5 protein used in MSA. Since a protein must interact with other biomolecules, hydrophobic patches help in the recognition and association of interacting molecules (Patel et al., 2012). The six observed patches help the target protein to interact with others to carry out its functions. Therefore, the binding of AdoHcy on His45 hydrophobic patch in yellow color (Figure 9) may inhibit the binding of another molecule, which is important for the function of Mouse ZMYND19. Since histidine plays a role in the folding of ZMYND19 (Michalek et al., 2011), its interruption while binding with AdoHcy ligand, will prevent protein from folding, therefore the protein cannot function. It was reported that AdoHcy is naturally a potent feedback inhibitor of all S-adenosyl-L-methionine (AdoMet) dependent methylation reactions (Witvrouw et al., 1997). This methylation is vital for Mouse ZMYND19 sorting from cytoplasm to plasma membrane, to interact with MCHR1 which leads to cardiovascular diseases and obesity (Schatz, 1997). In addition, DNA methylation regulates gene expression involved in cell growth, therefore defects associated with the DNA methylation result in cancer (Francke et al., 2005). In light of Liebert (Liebert et al., 2007), this present study suggested that the binding of AdoHcy to Mouse ZMYND19 will prevent it from being sorted and hinder its interaction with MCHR1 and eventually prevent cardiovascular and obesity diseases. In accordance with findings of Maruyama (Francke et al., 2005) and the fact that Mouse ZMYND19 is suggested to be involved in protein-protein interaction of a number of transcriptional co-repressor proteins, where its defects result in cancer (Du et al., 2014). This binding of AdoHcy to Mouse ZMYND19 can hinder its function thus serves as a good starting point to design a potent drug that can help treating diseases discussed in this manuscript.

4. Conclusion

Thus, this study suggested that the binding of AdoHcy to Mouse ZMYND19 will prevent it from being sorted and hinder its interaction with MCHR1 and eventually prevent cardiovascular diseases and obesity. Interestingly, Histidine45 functions in ZMYND19 folding, where its defect blocks the accurate folding
of ZMYND19. Therefore, interfering His45 with AdoHcy can prevent over expression of ZMYND19 which is highly suspected to cause cancer. In brief, this study can be useful in the development of potent drugs that can treat cancers, cardiovascular diseases, and obesity. However, it is recommended to perform molecular dynamics simulation prior to undertake in vivo analyses leading to synthesis of a novel drug.

**Conflict of interest**

All authors declare no conflict of interest

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