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Prediction of the binding mechanism for DNA methyltransferase 3A selective inhibitor using molecular simulation approach

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DNA methyltransferase(DNMT) catalyzes the methylation reaction in the DNA cytosine, and several isoforms have been reported, such as DNMT1 and DNMT3A. Although the overall structure of DNMT1 and DNMT3A are different, the active sites of both proteins are similar to each other [1]. DNA methylation is involved in the inhibition of gene expression, and DNMT hypermethylation is related to the formation and progression of cancer cells since it causes inhibition of the tumor suppressor gene [2]. To prevent hypermethylation, many DNMT inhibitors have been developed. Especially, inhibitors which bind selectivity to specific a DNMT isoform are attractive because selective drugs are expected to have few side effects [3].

Halby L *et al.* [4] have reported a selective inhibitor can bind to DNMT3A with about 100 times more activity than DNMT1. However, the molecular mechanism of selectivity is still unknown because the complex structure of DNMT3A and any selective inhibitor has not been clarified.

In this study, we predict the complex structure and the residues responsible for binding selectivity by molecular simulation. Docking simulations were first carried to generate initial structures of several candidate complexes, and MD simulations were performed to relax the structures and analyze the stability of complexes. The most stable complex structure was determined by RMSD analyze and the binding free energy using MM/PBSA method. Finally, we analyzed the energetic contribution of each residue of the protein, interactions, and the structural difference with DNMT1. Binding free energy and interaction analysis are suggested that VAL665 and ARG688 of DNMT3A form an interaction with selective inhibitor. Because these residues are replaced by MET1169 and ASN1192 in DNMT1, compounds that interact with VAL665 and ARG688 may selectivity inhibit DNMT3A. In conclusion, we have predicted the complex structure of a DNMT3A–selective inhibitor and the cause of its binding selectivity.

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