Allosteric Site in MetAP-II Explored by Markov State Model-Based Adaptive Sampling Molecular Dynamics Simulations

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Abstract

Methionine aminopeptidase-II is a metalloprotease, primarily responsible for the co-translational removal of N-terminal initiator methionine from the nascent polypeptide chain during protein synthesis. MetAP-II has been involved in angiogenesis and endothelial cell proliferation which ultimately is considered a target of angiogenesis and cancer. Therefore, inhibition of MetAP-II could be a new therapeutic approach for the treatment of cancer. However, there is no effective drug available for cancer involving MetAP-II. Here, by combining Markov State Model-based Adaptive Sampling molecular dynamics simulations to ligand-free and ligand-bound MetAP-II along with small molecule ring fragments screening on metastable states, we attempted to explore the allosteric behavior of the disordered loop region that is missing in most of the crystal structures. This loop region has a direct signal to the binding site and follows a single route. Further analysis using different tools confirms the druggability of the pocket that is formed due to this loop region. These findings are expected to pave the new way for the MetAP-II inhibition method by designing allosteric inhibitors.

Introduction

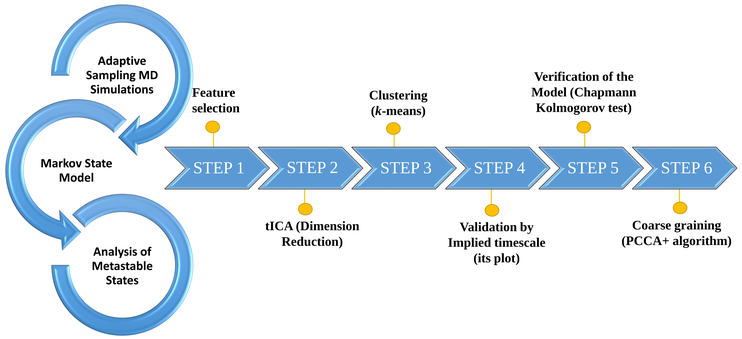
Cancer is not meant to be just killing the tumor cells, there are other approaches as well to fight cancer, for instance, the anti-angiogenic method. The inhibition of angiogenesis also helps in treating the solid tumor which is a significant approach for killing tumor cells.

Methionine aminopeptidase-II is an angiogenic target, involved in tissue repairing, angiogenesis, cancer, endothelial cell proliferation, protein synthesis, and protein degradation. High expression of this gene is found almost in all types of cancers including mesothelioma, lymphomas, colorectal adenocarcinoma, hepatoma, neuroblastoma, etc. Although there is no FDA-approved drug available against this enzyme.

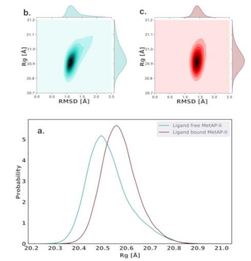
Objective

To evaluate the role of the disordered loop region during the methionine aminopeptidase-II inhibition process.

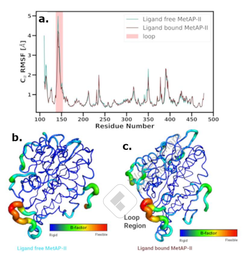
Methodology



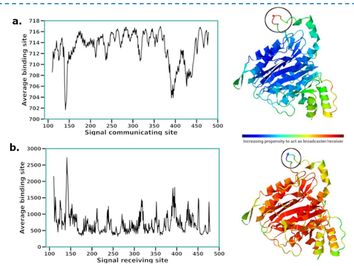
Results and Discussion



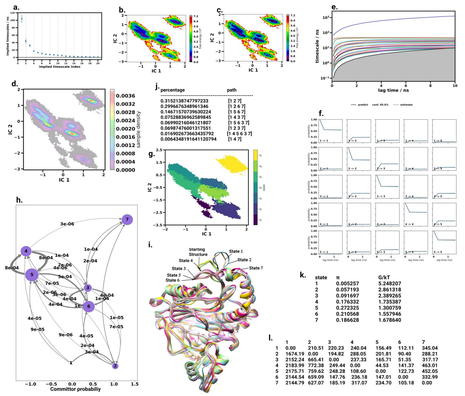
Compactness of MetAP-II: (a) Radius of gyration, (b) RG/RMSD in ligand-free, and (c) RG/RMSD in ligand-bound MetAP-II.



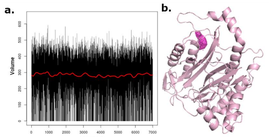
Flexibility in MetAP-II: (a) RMSF of each amino acid residue, (b) 3D-representative of ligand-free, and (c) Ligand-bound MetAP-II.



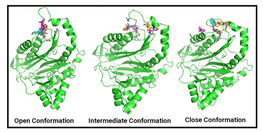
Allosteric behavior of the loop region: (a) Signal communication efficiency, and (b) Signal receiving efficiency of each amino acid residues of MetAP-II.



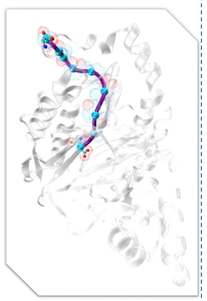
Markov State Model: (a) Ev/its index, (b) Free energy landscape (FEL), (c) Clusters in FEL, (d) Density probability plot, (e) ITS plot, (f) Chapmann-Kolmogorov plot, (g) Macrostate distribution, (h) Flux analysis, (i) 3D-Representative of each macrostates, (j) Pathway analysis result, (k) Population and its energy, (l) Mean first passage time.



Pocket volume Detection: (a) Volume of pocket in each ensembles obtained from markov state model analysis, and (b) 3D-representation of MetAP-II displaying pocket at the loop region.



Druggability: Consensus clustered of the small fragments at the selected metastable states of the methionine aminopeptidase-II.



Signaling pathway from the identified loop region to the active site of MetAP-II:

Conclusion

Adaptive-sampling-based Markov state model on MetAP-II explored the allosteric loop region which demonstrated a kind of found to exist in open and close conformation. This loop region is more flexible in the ligand-free methionine aminopeptidase-II compared to the ligand-bound gating MetAP-II.

Future Perspectives

Allosteric inhibitors will be designed. → **Molecular dynamics simulations on allosteric inhibitor bound MetAP-II will be performed** → ***In-vitro* and *in-vivo* biological activity of the identified inhibitors will be carried out.**

References

- Folkman, J. (1996). "Fighting cancer by attacking its blood supply." Scientific American 275(3): 150-154.
- Pérez, A., P. Herrera-Nieto, S. Doerr and G. De Fabritiis (2020). "AdaptiveBandit: a multi-armed bandit framework for adaptive sampling in molecular simulations." Journal of Chemical Theory and Computation 16(7): 4685-4693

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