CALIFORNIA STATE SCIENCE FAIR
2013 PROJECT SUMMARY

Name(s)

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Project Number

S0519

Project Title

MD Simulations of Membrane-Bound Aromatase with Titrated Asp-309: Implications for Catalysis and Novel Inhibitors

Abstract

Objectives/Goals

This study's objective is to 1) Discover novel druggable sites absent in the crystal structure of aromatase by incorporating flexibility with molecular dynamics (MD) simulations; 2) Elucidate the role of Asp-309 and its protonation state in the structural features of the active site, active site channels, water networks, and catalysis; 3) Develop a general framework for the next-generation inhibitors targeting novel druggable sites.

Methods/Materials

Two protein-membrane systems (sampling the two protonation states of Asp-309) was computationall modeled using CHARMM-GUI and Maestro. NAMD 2.7b on the SDSC Trestles and TACC Ranger supercomputers ran minimization and equilibration of the systems, as well as two 250-nanosecond trajectories of free molecular dynamics. The resulting data was analyzed and visualized using GROMACS, VMD, UCSF Chimera, and Tcl scripts. FTMap performed computational solvent mapping, and MOLE 2.0 analyzed active site channels.

Results

The model and the procedure for modeling membrane proteins was validated with experimental data, proving its efficiency and accuracy. The active site channel, heme proximal cavity, and active site crevice were identified as novel druggable sites absent in the crystal structure, and the overlapping of solvent probes enabled the development of preliminary novel inhibitor scaffolds. Furthermore, the protonation state of Asp-309 was implicated in major reshaping of the active site and its channels, improving the understanding of aromatase catalysis.

Conclusions/Discussion

The modeling procedure used in this study can be applied to other important membrane proteins implicated in major diseases like cancer and HIV/AIDS. Furthermore, incorporation of protein flexibility enabled the discovery of previously overlooked druggable sites, and enabled the development of novel inhibitor scaffolds targeting these new sites. Lastly, improved understanding of the role of Asp-309 allows for greater insight into the mechanism of action of aromatase, as well as potential for inhibitors that manipulate the protonation state of Asp-309.

Summary Statement

By incorporating protein flexibility and a membrane to aromatase, I discovered novel druggable sites on aromatase, developed novel inhibitor scaffolds, and elucidated the role of Asp-309.

Help Received

Dr. Rommie Amaro mentored my project and allowed me to access the computational resources available to the Amaro Lab. Additionally, she and Dr. Luke Czapla answered any questions I had, gave me advice, suggested various things, helped me with programs, and edited my report.