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Mechanisms of drug resistance of taxol based on computational studies

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Statement of the Problem: Microtubules are made up of α-β stacked units known as tubulin heterodimers. The dynamics of how the microtubules grow and shrink will affect how cell division occurs. With the great success of Paclitaxel and Docetaxel drugs for cancer treatment, microtubule-stabilizing agents (MSAs) have gained substantial attention for the discovery of next-generation anticancer agents. However, drug resistance is a major challenge associated with these agents and for the overall response and survival of cancer patients. It is important to study the binding kinetics and binding mechanisms among tubulin dimer, the microtubule-targeting drugs, and microtubule-associated proteins, because this information will assist us to understand how drugs and drug resistance change the dynamics of MT association/dissociation, and thereby develop anticancer therapies.

Methodology & Theoretical Orientation: Docking was performed on the structures with the Taxol bound. All ligands were then docked flexibly to seek the most energetically favorable ligand conformation. The most favorable poses were recorded. The ligands from various poses after docking simulation were overlapped. MD simulations will be performed for different bound conformations and different mutants. The results will provide better understanding of the mechanisms of drug resistances.

Conclusion & Significance: The docking results confirmed and identified some significant binding residues. We will examine if the specified amino acid residues will confer with drug resistance.

Biography

Zhong-Ru (Paul) Xie created a novel docking scoring function which is the first method using graph theory in docking and a novel drug binding site prediction method which achieves the best prediction accuracy so far. He also wrote a chapter reviewing the progress of this topic. Therefore, he not only has the expertise in the interactions between protein and the known/potential drugs, but also understands how the docking algorithms function very well. He also has the expertise in kinetic modeling and molecular dynamic (MD) simulation which can assist to understand the kinetics of drug binding, the dynamic interactions, and the mechanism of drug resistances.

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