"Computational cancer chemotherapy drug design and laboratory validation"

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Abstract

The structural protein, β-tubulin is the target for a number of anti-mitotic compounds that bind to and inhibit microtubule dynamics, leading to apoptosis in all dividing cells. The existence of several isotypes of β-tubulin, coupled with their varied distribution in normal and cancerous tissues provides us with a platform upon which to construct novel chemotherapeutic agents that are able to differentiate between normal and cancerous cells. A drug that targets those tubulin isotypes specifically expressed in tumor cells would maintain its cytotoxic activity on these cancerous cells, yet have a reduced effect on dividing cells in normal tissue, resulting in a reduction of side effects. We have performed homology modeling of approximately 500 α- and β-tubulin sequences and identified an expected global, structural similarity of tubulin monomers. We have been able to calculate discernable differences in several properties, including their net electric charge, volume, surface area, dipole moment and dipole vector orientation. These are properties that may influence the functional characteristics of individual tubulin monomers, thereby resulting in a global effect on microtubule stability and assembly kinetics. Using these homology models, we have obtained a consensus set of nine human β-tubulin isotypes and analyzed them for differences within the previously characterized paclitaxel, colchicine and vinblastine binding sites. Several colchicine and paclitaxel derivatives were then computationally designed and their binding to the isotypes tested Quantum Mechanics and Molecular Mechanics modeling experiments. Using these techniques, a clear differentiation between the tubulin isotype being considered and relative binding affinities for each of these derivatives was observed. These computationally based experiments have provided us with a small virtual library of drug structures that have increased binding affinity towards specific tubulin isotypes. This library is now being used to direct the synthesis and testing of these drugs, both *in vitro* and *in vivo*, to determine their effect on different tubulin isotypes. Small scale testing of these compounds on a number of primary tumour cell cultures has produced promising results for their ability to selectively target specific cancer cells. In this presentation, the preliminary results of our computational and experimental studies will be summarized. The achieved correlation between theoretical prediction and laboratory assay outcomes is very encouraging.