Entry of taxol into the microtubule lumen: estimation of diffusion rates across nanopores using Brownian dynamics.

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Abstract

Microtubules are long, dynamic cytoskeletal components, which are stabilized by the binding of drugs such as paclitaxel; thus these drugs have been commonly used in cancer patients for their antimitotic properties. I am investigating the influence of the tubulin isotype on the rate of binding of paclitaxel to the microtubule. We hope in this way to explain differences in drug susceptibility between cells with different tubulin forms. Experimental evidence suggests that taxol may gain access to its tubulin binding site by entering through pores between individual tubulin dimers in the microtubule walls. Molecular modeling of these pores shows that cross-sectional dimensions are comparable in size to the taxol itself and indicates that taxol must take advantage of its flexibility to assume an extended conformation allowing for passage. We are investigating whether tubulin isotype composition may influence the rate of taxol entry through microtubule pores. We hope in this way to demonstrate the effect of size on the design of more potent taxol analogs, as well as provide a knowledge of the effect of pore size on the localization of taxol in various cell types, useful for the consideration of harmful drug side effects. We will analyze various pores from the different microtubule structures and select the ones showing greatest differences to use in Brownian

dynamic simulation studies. We are working on applying the Brownian dynamics utility implemented in the SDA program package to estimate the mean rate of passage of taxol through the pores. Such a computational study should allow this proposed means of entry to be evaluated, and compared for different tubulin isotypes.