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Mitotic Checkpoint Function and Cancer Cell Chemosensitivity

Microtubules are intracellular protein fibers involved in cell architecture as well as the movement of many kinds of particles in the cell. Many cancer patients are treated with drugs such as paclitaxel (Taxol), docetaxel (Taxotere) or vinorelbine (Navelbine) that inhibit the dynamic assembly and disassembly of microtubules. In cancer cells the major therapeutic target of these drugs is believed to be the mitotic spindle microtubules involved in moving replicated chromosomes in dividing cells. In the presence of such drugs the capture of replicated chromosomes by the mitotic spindle is grossly inefficient. In normal cells the presence of a single chromosome that has failed to achieve correct attachment to the mitotic spindle results in a signal for cell cycle arrest (mitotic arrest) to prevent premature completion of mitosis. In many cancer cells this stop signal is ineffective and contributes to genetic instability, a hallmark of human cancer.

In this proposal we have made two related hypotheses. First, that tumors that lack an intact mitotic checkpoint have undergone *in vivo* selection to tolerate chromosomal instability and therefore will be inherently resistant to antimicrotubule drugs. Second, that tumor cells that are competent for mitotic arrest can be made hypersensitive to antimicrotulubes by acute inactivation of the mitotic checkpoints. The results of these experiments will aid in the design of more effective treatment strategies for cancer patients.