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Titel des Beitrags: In vivo measurement of microtubule dynamics using stable isotope labeling with heavy water. Effect of taxanes.

Abstract:
Microtubules are dynamic polymers with central roles in the mitotic checkpoint, mitotic spindle assembly, and chromosome segregation. Agents that block mitotic progression and cell proliferation by interfering with microtubule dynamics (microtubule-targeted tubulin-polymerizing agents (MTPAs)) are powerful antitumor agents. Effects of MTPAs (e.g. paclitaxel) on microtubule dynamics have not yet been directly demonstrated in intact animals, however. Here we describe a method that measures microtubule dynamics as an exchange of tubulin dimers into microtubules in vivo. The incorporation of deuterium (\((2)H(2)\)) from heavy water (\((2)H(2)O\)) into tubulin dimers and polymers is measured by gas chromatography/mass spectrometry. In cultured human lung and breast cancer cell lines, or in tumors implanted into nude mice, tubulin dimers and polymerized microtubules exhibited nearly identical label incorporation rates, reflecting their rapid exchange. Administration of paclitaxel during 24 h of \((2)H(2)O\) labeling in vivo reduced \((2)H\) labeling in polymers while increasing \((2)H\) in dimers, indicating diminished flux of dimers into polymers (i.e. inhibition of microtubule dynamic equilibrium). In vivo inhibition of microtubule dynamics was dose-dependent and correlated with inhibition of DNA replication, a stable isotopic measure of tumor cell
growth. In contrast, microtubule polymers from sciatic nerve of untreated mice were not in dynamic
equilibrium with tubulin dimers, and paclitaxel increased label incorporation into polymers. Our results
directly demonstrate altered microtubule dynamics as an important action of MTPAs in vivo. This
sensitive and quantitative in vivo assay of microtubule dynamics may prove useful for pre-clinical and
clinical development of the next generation of MTPAs as anticancer drugs.

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