New Mechanisms for Old Chemotherapy Drugs

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Cancer chemotherapeutic drugs can be broadly divided into cytoxic, hormonal and targeted, but new modalities are needed to combat metastatic disease. We are approaching this problem by analyzing the biochemical and cellular mechanisms of successful and failed drugs. Anti-microtubule drugs such as paclitaxel are though to selectively kill dividing cells via mitotic arrest. We compared responses to anti-microtubule and targeted anti-mitosis drugs in cell culture and xenograft models using single cell imaging. We propose that the mechanism in common to the two drug classes, death via mitotic arrest, is responsible for the anti-proliferative side effects of chemotherapy. Tumor killing efficacy appears to arise from a novel interphase cell killing pathway unique to the anti-microtubule drugs and the tumor environment, which we are trying to recapitulate in cell culture. Another approach to chemotherapy is to activate tumor resident innate immune cells to damage the tumor. We have analyzed the mechanism of the anti-tumor flavonoids FAA and DMXAA that cure mouse tumors by this mechanism, but failed in man. We have identified a candidate protein target in mouse macrophages, and find that the human homolog does not bind the drugs, which may explain lack of efficacy in man. These studies identify a promising target for a new class of chemotherapy drugs that works by activating innate immunity.