Antiangiogenic drugs impede chemotherapy-stimulated tumor recovery

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Scientists have gained new insight into a mechanism whereby chemotherapy may actually assist the rapid regrowth of tumors after treatment. The research, published by Cell Press in the September issue of the journal *Cancer Cell*, also helps to explain why a combination of traditional chemotherapy with drugs that block formation of new blood vessels might impede the devastating tumor recovery that often follows cancer therapy.

"Chemotherapy remains the most commonly employed form of systemic cancer treatment. However, although partial or complete shrinkage of tumor mass is frequently induced in chemotherapy-responsive tumors, survival benefits of such responses can be compromised by rapid regrowth of the drug-treated tumors," says senior study author Dr. Robert S. Kerbel from the University of Toronto.

Clinical trials have indicated that drugs that inhibit the growth of blood vessels, called antiangiogenic drugs, can sometimes enhance the effectiveness of traditional chemotherapy. For example, coadministration of the antiangiogenic drug bevacizumab with the chemotherapeutic agent paclitaxel improves survival benefits for metastatic breast cancer and small cell lung cancer. In contrast, coadministration of bevacizumab with gemcitabine for treatment of pancreatic cancer does not increase the effectiveness of chemotherapy alone.

"Several hypotheses have been proposed to explain how antiangiogenic

drugs enhance the treatment efficacy of cytotoxic chemotherapy, including impairing the ability of chemotherapy-responsive tumors to regrow after therapy," says author Dr. Yuval Shaked. Drs. Kerbel, Shaked, and colleagues had previously shown that treatment with a type of cytotoxic-like agent known as a vascular disrupting agent (VDA) induces rapid mobilization of cells called circulating endothelial progenitors (CEPs) from the bone marrow compartment that helps the tumor to regrow blood vessels and thereby recover from treatment.

The researchers built on this earlier observation by analyzing whether different, conventional chemotherapeutic drugs had variable abilities to impact CEP mobilization and whether antiangiogenic drugs could block chemotherapy-induced CEP responses and hence amplify their effectiveness. They found that paclitaxel rapidly induced CEP mobilization whereas gemcitabine did not. They went on to show that pharmacological inhibition of CEP mobilization by combination treatment with an antiangiogenic drug or treatment of mutant mice deficient in CEPs resulted in enhanced antitumor effects mediated by paclitaxel but not gemcitabine.

"Our results provide a new perspective regarding the impact that conventional chemotherapy can have on tumor angiogenesis and hence how combination with antiangiogenic drugs may amplify the antitumor effects of chemotherapy," explains Dr. Kerbel. "Further, our findings provide a potential explanation of why not all chemotherapy drugs will necessarily have their efficacy enhanced by the addition of an antiangiogenic agent when the mechanism involves blunting CEP mobilization acutely induced by the chemotherapy drug."

Source: Cell Press