Solid tumor cells not killed by radiation and chemotherapy become stronger

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Because of the way solid tumors adapt the body's machinery to bring themselves more oxygen, chemotherapy and radiation may actually make these tumors stronger.

"In a sense, these therapies can make the tumor healthier," said Mark W. Dewhirst, D.V.M., Ph.D., professor of radiation oncology at Duke University Medical Center. "Unless the treatment is very effective in killing many if not most tumor cells, you are shooting yourself in the foot."

Dewhirst and colleagues Yiting Cao, M.D., Ph.D., of Duke Pathology, and Benjamin Moeller, M.D., Ph.D. have introduced this counter-intuitive idea at recent conferences and in a review article featured in the June issue of *Nature Reviews Cancer*.

Radiation and chemotherapy do kill most solid tumor cells, but in the cells that survive, the therapies drive an increase in a regulatory factor called HIF1 (hypoxia-inducible factor 1), which cells use to get the oxygen they need by increasing blood vessel growth into the tumor. Solid tumors generally have low supplies of oxygen, Dewhirst explained and HIF1 helps them get the oxygen they need.

The review article concludes that blocking HIF1 would provide a clear mechanism for killing solid-tumor cells, particularly cells that are proving resistant to radiation or chemotherapy treatments.

As a part of this work, Dewhirst's team has been studying the phenomenon of rising and falling oxygen levels in tumors, called cycling hypoxia. Oxygen levels have been found to naturally cycle up and down in individual blood vessels as well as large tumor regions. This instability in the tumor's oxygen levels can increase HIF-1 production and cause radiation therapy to fail, Dewhirst said.

"It is my opinion that the whole tumor grows more aggressively because of this pulsation of oxygen at low levels," Dewhirst said. "Most people thought cycling hypoxia was caused by temporary stoppage of blood flow in single blood vessel in tumors. In fact, however, oxygen levels cycle up and down virtually everywhere in the tumor, which is caused by fluctuations in blood flow rate. It has been a challenge to convince people of this."

Dewhirst and colleagues have made movies of oxygen transport in a tumor of a living animal that show the oxygen levels cycle up and down significantly, pulsing in waves seen as color changes in the movies. (View these movies at the *Nature Reviews Cancer* site: http://www.nature.com/nrc/journal/v8/n6/suppinfo/nrc2397.html)

The Duke team argues that blocking HIF1 is the consistent answer to tumor growth problems. Blocking HIF1 activity interferes with the tumor's ability to undergo glycolysis (energy production) in low-oxygen conditions, which blocks tumor growth, the authors wrote. Exactly how to accomplish chemotherapy or radiation treatment in the safest, most effective ways, in combination with HIF1 blockade, is still open for exploration, Dewhirst said.

For example, targeting HIF1 in the early stages of tumor growth, especially in very early cancer spread, may help, Dewhirst said. "For a woman who has had a primary breast tumor removed, and who is at high risk for cancer spread, this might be a situation in which you'd target

HIF1," he explained. "Blocking HIF1 makes sense during the early stages of angiogenesis, which is the accelerated phase of blood vessel formation. In this way, you could keep the early metastasis sites inactive and prevent them from growing."

The Duke team has completed a phase I trial with a HIF1 inhibitor. "We are actively pursuing this clinically and will be moving this study into Phase 2," Dewhirst said. "We are interested in other applications of HIF-1 inhibition in combination with radiation and chemotherapy for different diseases."

Source: Duke University Medical Center