MedicalXpress

Normalizing tumor vessels to improve cancer therapy

August 25 2008

Chemotherapy drugs often never reach the tumors they're intended to treat, and radiation therapy is not always effective, because the blood vessels feeding the tumors are abnormal—"leaky and twisty" in the words of the late Judah Folkman, MD, founder of the Vascular Biology program at Children's Hospital Boston.

Now, Vascular Biology researchers have discovered an explanation for these abnormalities that could, down the road, improve chemotherapy drug delivery. Their findings were published in the August 12 issue of the *Proceedings of the National Academy of Sciences*.

A tumor's capillaries—small blood vessels that directly deliver oxygen and nutrients to cancer cells—are irregularly shaped, being excessively thin in some areas and forming thick, snarly clumps in others. These malformations create a turbulent, uneven blood flow, so that too much blood goes to one region of the tumor, and too little to another. In addition, the capillary endothelial cells lining the inner surface of tumor capillaries, normally a smooth, tightly-packed sheet, have gaps between them, causing vessel leakiness.

"These abnormal features of tumor vessels impair delivery of circulating chemotherapeutic drugs to the actual tumor site" says Kaustabh Ghosh, PhD, first author on the paper, and a postdoctoral fellow in the laboratory of Donald Ingber, MD, PhD, the paper's senior author and interim co-director of the Vascular Biology program.

The idea of a therapy aimed at normalizing a tumor's blood vessels, to ensure that chemotherapeutic agents reach the tumor, has already been explored, but these attempts have only targeted soluble factors, particularly vascular endothelial growth factor (VEGF). Tumors secrete VEGF in abundance; it not only promotes blood vessel growth (angiogenesis), but makes them leaky. While blocking VEGF action helps reduce leakiness and improves vessel function, the effects have been transient, Ghosh says.

Ghosh and Ingber took a different approach, focusing on the role of mechanical forces on tumor blood vessels, which had previously been ignored. Past studies by Ingber and colleagues have shown that a capillary cell's sensitivity to soluble angiogenic factors like VEGF—and subsequent blood vessel formation—are determined by the mechanical balance between the cell's internal state of tension or contraction, and that of the surrounding support structure, or matrix, to which the cell adheres. These forces guide normal vascular pattern formation. Because tumor vessels are malformed, Ghosh wondered whether tumor capillary cells have lost the normal cells' ability to sense and respond to changes in matrix stiffness and distortion.

To address this question, the researchers studied capillary cells isolated from mice prostate tumors, provided by Andrew Dudley, PhD, in the lab of Michael Klagsbrun, PhD, in the Vascular Biology Program, and exposed them to cyclic mechanical stress—mimicking the pulsatile nature of blood flow and matrix distortion resulting from rhythmic heart beats. They found that normal capillary cells aligned themselves uniformly perpendicular to the force direction, but most of the tumor capillary cells failed to reorient, says Ghosh. These cells were "all over the place," and due to this lack of alignment, gaps appeared between neighboring cells, which may explain the increased vessel permeability.

Ghosh and colleagues also found that tumor capillary cells sense and

respond to matrix rigidity differently than normal cells. When placed on a stiff surface, mimicking the tumor matrix, the cells tended to keep spreading even after normal capillary cells stopped doing so. Because of these differences in "mechanosensing," the tumor capillary cells were able to form capillaries even when cell densities were very low, while normal cells failed to do so. At higher cell densities, normal cells formed nice capillaries, whereas the tumor cells balled up into tangled clumps, creating the irregular patterns seen in many images of tumor blood vessels. "Because high cell density increases contractility across the entire cell layer, these findings suggested that tumor capillary cells are inherently hyper-contractile," says Ghosh.

The researchers went on to find that this hyper-contractility results from an increase in the levels of a protein called Rho-associated kinase (ROCK), which controls tension within the cell. When they treated tumor capillary cells with an inhibitor of ROCK, they normalized the behavior of the tumor capillary cells, so that the treated cells exhibited near-normal mechanical responses and formed more regularly-shaped tubular vessels.

Source: Children's Hospital Boston