Taming physical forces that block cancer treatment

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A Massachusetts General Hospital research team has identified factors that contribute to solid stress within tumors, suggesting possible ways to alleviate it, and has developed a simple way to measure such pressures.

It's a high-pressure environment within solid tumors. Abnormal blood and lymphatic vessels cause fluids to accumulate, and the uncontrolled proliferation of cancer cells within limited space leads to the buildup of what is called solid stress. Both types of pressure can interfere with the effectiveness of anticancer treatments, but while strategies have been developed that reduce fluid pressures, little has been known about the impact of solid stress or potential ways to alleviate it. Now a Massachusetts General Hospital (MGH) research team has identified factors that contribute to solid stress within tumors, suggesting possible ways to alleviate it, and has developed a simple way to measure such pressures.

"Traditionally cancer research has focused on cancer cells and, more recently, on the biochemical microenvironment of tumors," says Rakesh Jain, PhD, director of the Steele Laboratory for Tumor Biology at MGH and senior author of the study in the Sept. 18 issue of Proceedings of the National Academy of Sciences. "Our work shows that the physical or mechanical microenvironment plays an equally important role in tumor progression and treatment resistance."

Jain and his colleagues have been leaders in understanding the impact of elevated fluid pressures that make it difficult for drugs to enter and

permeate tumors. Their work showed that fluid pressures are relieved when antiangiogenesis drugs normalize the abnormal blood vessels characteristically found within solid tumors, improving the effectiveness of other anticancer therapies. But that approach can only work if vessels have not been squeezed shut by solid stress in surrounding tissues. In recent studies Jain's team showed that solid stress also increases the invasiveness of cancer cells.

The current study was designed to develop techniques that measure solid stress in tumors, to identify factors that contribute to the generation of this solid stress and to determine whether previously compressed blood vessels would open when stress-inducing components were depleted. Based on predictions from mathematical models, the MGH-based team developed a remarkably simple way to measure solid stress within tumor tissues.

In experiments using both tumors experimentally grown in mice and tumors removed from human patients, the researchers found that, when a solid tumor is cut in two, each segment begins to swell along the sliced surface, releasing stored solid stress. In contrast, when a sample of normal tissue is cut in two, the separated halves of tissue retain their size and shape (links to video files below). Measuring the extent of shape relaxation along with other mechanical properties of tumor tissue enabled calculation of the amount of solid stress within a tumor sample.

Additional experiments utilizing the newly developed technique identified several components that contribute to increased solid stress within tumors, including the proliferation not only of cancer cells but also of fibroblasts and other components of the tumor's extracellular matrix. In pancreatic tumors implanted into mice, the researchers showed that inhibition of a pathway leading to the growth of fibroblasts reduced solid stress associated with tumor growth and opened up compressed blood and lymphatic vessels, which could both relieve fluid

pressure and improve the delivery of chemotherapy drugs.

The authors note that their results may explain why the use of antiangiogenesis drugs has not improved treatment of highly fibrotic tumors – including dangerous pancreatic, lung and breast cancers – and suggest that a strategy targeting both aspects of intratumor pressure should be explored. "Now that we have seen how tumors exploit physical forces to facilitate progression and treatment resistance, we need to learn how to tame these fluid and solid forces to improve treatment outcomes," says Jain, the Cook Professor of Radiation Oncology (Tumor Biology) at Harvard Medical School. "We urgently need to identify safe pharmaceutical agents that reduce solid stress and then add them judiciously to current treatments."

More information:
www.pnas.org/content/109/38/15101.full.pdf+html

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