# New ways to measure solid stress in tumors could lead to improved understanding, therapies

November 28 2016

Massachusetts General Hospital (MGH) investigators have developed new methods for mapping and measuring solid stress - the force exerted by solid and elastic components - within tumors, an accomplishment that may lead to improved understanding of those forces and their consequences and to novel treatment strategies. The team from the Steele Laboratories of Tumor Biology in the MGH Radiation Oncology Department report their findings in the inaugural issue of *Nature Biomedical Engineering*.

"It has long been known that tissue stiffness is higher than normal in fibrotic tumors - tumors containing significant amounts of collagen and other connective tissues - and that has been linked to several hallmarks of cancer, including tumor growth, invasiveness and metastasis," says Rakesh K. Jain, PhD, director of the Steele Laboratories and corresponding author of the paper. "Solid stress is different from stiffness: It is the mechanical force transmitted within fibrotic tumors, and like a compressed spring, it accumulates and is stored as elastic energy within a tumor as it grows."

Jain's team discovered the first evidence of solid stress in tumors in 1997 and provided the first measurements in 2012. In numerous studies they have shown that the compression of blood and lymphatic vessels by solid stress contributes to tumor progression by impairing the supply of oxygen, which reduces the effectiveness of chemotherapy, immunotherapy and radiation treatment. More recently they found that the application of solid stress to tumors in living animals directly stimulates pathways involved in the initiation and migration of tumors. Strategies to alleviate solid stress by reducing collagen and hyaluronic acid, two primary structural components of the extracellular matrix that carry stress, have led to new approaches to enhancing the results of conventional therapies, which are currently being tested in an MGH clinical trial.

The Nature Biomedical Engineering paper describes the team's development of experimental and mathematical frameworks providing two-dimensional mapping of solid stress in tumors; sensitive estimation of the low levels of solid stress within small tumors, such as metastases; and the ability to quantify solid stress in tumors in living animals. All these methods were based on the concept of cutting the tumor and, as the stresses stored during tissue growth are released, high-resolution measurement of the tissue deformation with ultrasound or optical microscopy.

Using these methods to make measurements in mouse models of both primary and metastatic tumors, as well as in a few human tumor samples, revealed that solid stress and stored elastic energy may be different in primary and metastatic tumors, since they depend on both tumor cells and the surrounding microenvironment. Tumors with higher elastic energy are not necessarily stiffer, and vice versa; solid stress increases as tumors grow larger, and the normal tissue surrounding a tumor contributes significantly to solid stress.

"Two drugs are now in clinical trials based on their ability to release the mechanical forces exerted on tumor blood vessels by targeting collagen and hyaluronic acid," says Jain, who is the Cook Professor of Radiation Oncology (Tumor Biology) at Harvard Medical School. "Similar to the methods we previously developed to measure solid stress, these new methods could also be used to measure the results of solid-stress-reducing agents."

He adds, "The characterization of solid stress would also be beneficial in treatment of cancer in obese patients. We recently found that cooperation between fat cells, immune cells and fibroblasts in pancreatic tumors exacerbates the fibrotic microenvironment in obese patients, further promoting blood vessel compression. This is probably the most significant consequence of solid stress identified to date, and characterizing the response to agents designed to alleviate solid stress could improve the dismal outcomes of this often-deadly cancer."

**More information:** Solid stress and elastic energy as measures of tumour mechanopathology, *Nature Biomedical Engineering*, nature.com/articles/doi:10.1038/s41551-016-0004

Provided by Massachusetts General Hospital