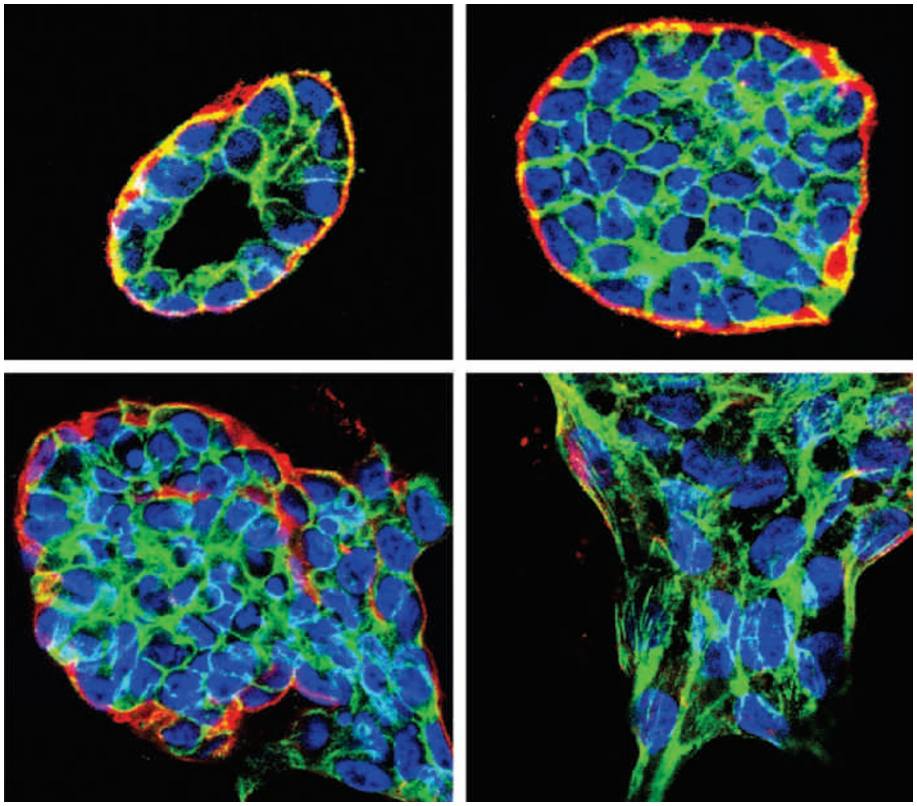

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The environment affects how cells develop, with greater stiffness leading to more cancer-like behaviour.

MECHANICS

The forces of cancer

The way cells physically interact with each other and their environment could help researchers understand the invasion and metastasis of solid tumours.

BY ERIKA JONIETZ

Hippocrates first used the term 'carcinoma' to describe cancerous tumours more than 2,000 years ago. But until the end of the nineteenth century, doctors knew little about solid tumours other than how much stiffer they were than the surrounding tissue. Even now, one of the most common ways people detect cancer is by discovering a lump. Yet despite the obvious contrast in hardness between a tumour and the surrounding tissue, the differences between their physical properties have largely been overlooked.

In the past 30 years, however, researchers have shown that the forces generated by, and acting on, tissues influence the way tumours grow, develop and metastasize. These forces may even be as influential as the genetic and molecular changes at the focus of modern cancer research. "From a clinical perspective, it is not at all unimaginable that there is a connection between the mechanics of tumours and their underlying biology," says physicist Jan T. Liphardt of the University of California, Berkeley, who heads the Bay Area Physical Sciences–Oncology Center.

In living organisms, cells are continuously exposed to physical forces, such as compression, tension, hydrostatic pressure and shear stress. They respond by modifying their behaviour and generating their own forces. "We're finding these forces are key to the way cells divide, interact, signal, move and attach," says Muhammad Zaman, a biomedical engineer at Boston University in Massachusetts. "There is a deeper appreciation now that cells are very touchy-feely — they're not just these things that receive and process signals." Such realizations have led to a new subfield in cancer research: physical oncology, a cross-disciplinary area aimed at exploring the physical laws that affect the development and behaviour of cancer in the hope of discovering therapies and diagnostics.

Physical forces are especially important in invasion and metastasis, the processes that make most cancer lethal. Researchers are investigating how forces from both within and outside developing cancer cells interact in intricate feedback loops. This work uses both well-established and novel tools, from atomic force microscopy and three-dimensional cell culture to fluorescent beads that track how cells change their environment.

SOFT CELLS

Research in cancer physics can be divided into two basic camps. One group believes that the mechanical characteristics of malignant cells are broadly similar across all solid tumours — a theory that, if proven correct, could lead to universal approaches to diagnostics and therapeutic targets. The other group believes that although many cancers share some physical characteristics, most features will be affected by mechanical differences among the tissues of origin. If this second view is true, researchers might need to devise tests and treatments for a bewildering array of mechanical circumstances.

Josef A. Käs, a soft-matter physicist at the University of Leipzig in Germany, is in the first group: he believes that the properties he's finding in breast and cervical cancer cells are common across tumours. He hopes to identify physical attributes of cells that would allow doctors to recognize which tumours are more likely to metastasize, regardless of where they originate. He contends that finding shared mechanical features among different cancers could provide a simpler view of the disease than the molecular picture, which is becoming increasingly diverse. Unlike biologists, he says, "physicists take a reductionist view".

The Käs lab has developed a device — he calls it an 'optical stretcher' — that determines how much a cell can be deformed in order to assess its elasticity and contractility; a cell's ability to contract is essential for movement and proliferation. Unlike tools such as optical tweezers and atomic force microscopes, the optical stretcher, which uses two laser beams pointed towards each other, can quickly measure the properties of thousands of cells. Käs has found that the elasticity and contractility of human breast epithelial cells change as they progress from normal to cancerous to metastatic, with the cells becoming softer as disease advances[1].

Käs says the device can be used to assess the likelihood of a tumour metastasizing without having to do biopsies from distant sites. He also believes it could be possible to reverse both elasticity and contractility with a drug that 'freezes' cancer cells, increasing their stiffness to stop them metastasizing. In order to travel to other locations in the body, tumour cells must squeeze through small gaps in the extracellular matrix

around them and between the cells in blood-vessel walls; this is much easier for softer, more pliable cells. He says he is now working with a major pharmaceutical company to identify possible anti-metastatic drugs.

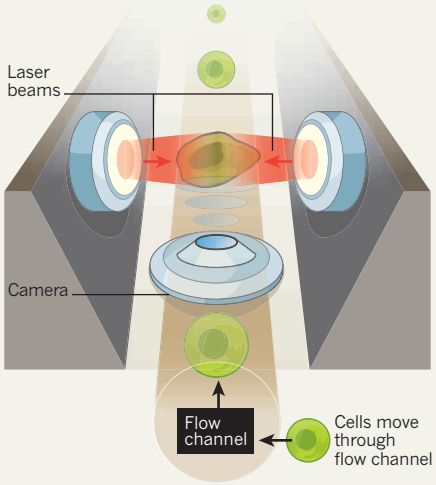
Similarly, Zaman thinks it should be possible to determine which physical parameters make cancer cells most likely to develop chemoresistance[2] by using a technique called microrheology, in which nanoparticles are injected into cells to quantify their viscosity and elasticity. This technique is suited to physical oncology, he says, because it can be used in three-dimensional (3D) cultures, which more closely approximate a tumour's environment in the body than the traditional 2D dish culture[3].

Cells grown in dish cultures are nearly always less resistant to cytotoxic agents than those grown in 3D matrices; the main difference, Zaman says, is the forces they experience. So he cultures cancer cells in different 3D environments (stiffer or softer, or with different drug concentrations) and measures the cells' physical properties to see which ones correlate with drug resistance. There are large numbers of variables, and researchers can measure only a few at a time, but Zaman thinks the results will ultimately help doctors decide which tumours are most likely to develop chemoresistance.

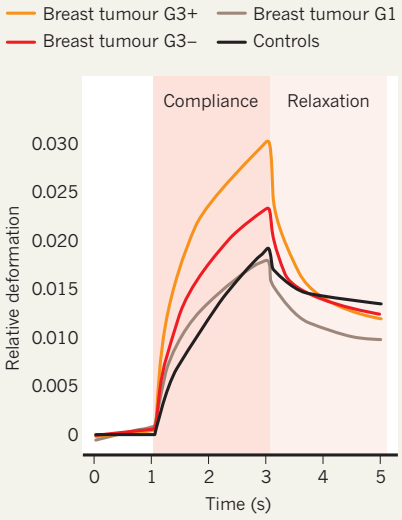
DIAGNOSING AT A DISTANCE

This optical stretcher uses two laser beams to measure cells' elasticity and contractility. Because advanced disease is associated with softer cells, the results could be used to assess whether a tumour is likely to metastasize.

Cells travel along a flow channel and are suspended in two opposing laser beams. As the laser beams are intensified, the camera takes a series of images of the cell.



Elasticity of normal breast cells and cells from tumours of increasing aggressiveness (stages G1–G3+). Cells from more aggressive tumours deform more easily.



MECHANICAL DIFFERENCES

It is not yet clear whether Käs and Zaman are correct in their belief that solid tumours represent a single physical system. Most physical oncology researchers hold the opposite view, believing that the forces generated by, and acting on, cancers vary among tumour types. Valerie Weaver, a bioengineer at the University of California, San Francisco, is in the latter group. Different tissues have different elastic properties, she says, which are created by interactions between tissue-specific cellular forces and the configuration of the proteins around them. "Disease is uniformly a corruption of the mechanics. But in each cancer, it's going to be different," says Weaver, who was one of the first to study 3D cultures of breast cancer cells.

Her lab is finding differences among the mechanics of many kinds of tumour, including brain, pancreas, breast and skin cancers. Brain tumours, for example, are soft, whereas pancreatic tumours are rigid. And because cells' surface receptors can be sensitive to physical or biochemical cues, or both, from their surroundings, Weaver believes it makes sense for variations in tissue type to affect how cancer cells behave. The cues are conveyed either physically or chemically through a cell's cytoskeleton to its nucleus, where they can influence which genes are expressed — an effect that can lead to conditions that promote disease. Some genes code for enzymes that can remodel the extracellular matrix, for example, digesting collagen to open a path for invading cancer cells.

Ben Fabry also compares the mechanics of cells from different cancers in an attempt to understand how they influence the course of disease. Fabry, a biophysicist at Friedrich-Alexander-Universität Erlangen-Nürnberg in Germany, has used fluorescent beads tightly embedded in collagen matrices to measure how various carcinoma cells affect their surrounding matrix, and to calculate their contractility[4]. Invasive breast and lung carcinoma cells turned out to be more contractile than non-invasive cells — but higher contractility does not always mean higher invasiveness. In fact, the most contractile cells Fabry has measured were from a non-invasive vulva carcinoma. He doesn't think the results are that surprising. Contrary to what Käs is finding, Fabry says: "Different cancers employ different invasion strategies, some of which benefit from a softer and more fluid-like cell phenotype, others from a stiffer phenotype; some use more contractile forces, others may use pushing forces; some cancer cells migrate collectively, others as individual cells."

The molecular mechanisms that cells use to sense and cause physical changes in their environment and in themselves — the same mechanisms that prompt them to turn cancerous — are only beginning to emerge. "One of the problems in the field of cancer mechanics is understanding and quantifying the interplay of mechanics and chemistry," says Liphardt. "When someone says, 'Oh, it's mechanics,' it's extremely likely that it's chemistry too, and vice versa."

Weaver recalls that DNA pioneer James Watson confronted her during a presentation she gave last year entitled "The Force Journey of a Cell". "He said: 'I don't see how this is going to change anything. I don't see how this is going to translate into a cure.' I told him: 'Mechanics is one of the most primitive signalling systems. It is so fundamental to life and multicellular systems that it can't *not* be involved in cancer.'"

But she concedes that Watson has a point. Today's rudimentary explorations of cancer mechanics are a long way from discoveries that will lead to new therapies. Researchers studying the physical forces involved in cancer, she says, must define and understand the molecular principles underlying every aspect of the interplay between cell context and mechanics, from the nanoscale to the tissue level. Until they grasp those fundamental principles and use them to inform cancer biology — finding therapeutic targets, for example, or determining prognosis — this cross-disciplinary domain of cancer and physics will, she says, remain a "side curiosity".

Cancer mechanics is still a fledgling field. Basic questions remain to be addressed, such as how tissue mechanics relate to risk, outcome, intervention and personalized therapies. Only then can researchers face the challenge of translating these insights into clinical applications. As Weaver says: "Our hard work is just beginning." ■

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