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Elastic clues in cancer detection

In vitro nanomechanical studies have shown that cultured cancer cells are elastically softer than healthy ones, and new measurements on cells from cancer patients suggest that this mechanical signature may be a powerful way to detect cancer in the clinic.

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The behaviour of cells — including the way they grow, spread and die in the body — depends on the mechanical feedback they receive from their surroundings[1–4]. Atomic force microscopes (AFM) can probe the response of individual cells to nanonewton forces, and detect displacements on the nanometre scale[5]. These measurements are potentially useful for detecting human disease states because *in vitro* studies have shown that cancer cells have much lower elastic stiffness than normal cells — a characteristic that is attributed to the ability of cancer cells to metastasize or spread[6–8]. To date, however, *ex vivo* measurements of the mechanical properties of cancer cells obtained from patients have not been reported.

On the *Nature Nanotechnology* website today, James Gimzewski and colleagues[9] from the University of California at Los Angeles report, on the basis of AFM measurements, that live metastatic cancer cells taken from the lung, chest and abdomenal cavities of the patient are nearly four times less stiff than benign cells that line the respective cavities. The results are in good agreement with earlier *in vitro* experiments[6–8], and they also correlate well with current testing methods, such as antibody labelling, which means that this mechanical signature could prove to be a useful biomarker and complementary approach for detecting cancer in a clinical setting.

When a normal cell transforms into a cancerous one, its shape and also its internal scaffolding, known as the cytoskeleton, changes. This leads to changes in stiffness and the ability for cells to attach, move and spread on substrates. Furthermore, these alterations can also change the way cells invade and colonize new tissues. These modifications are typically diagnosed by surgically removing the tissue samples, placing thin sections of the tissue on a glass slide, staining and examining them under a microscope for manifestation of the disease. Additional tests that use antibodies to label specific markers or proteins on the cancerous tissue are also used to distinguish these cells from normal tissue. However, this complex process of cancer diagnosis is not always 100% accurate because normal cells can sometimes look like cancerous cells. Being able to quantify these changes using nanomechanical assays in conjunction with microscopic examination could, therefore, prove useful for detecting cancer in fluids obtained from cavities inside the body, which is where cancer cells often start to spread from.

Previous *in vitro* studies involved immobilizing cultured human cell lines on artificial substrates. Although this approach is useful, in the absence of an appropriate biochemical environment, the cells can exhibit different mechanical properties. Moreover, it is often difficult to obtain a good control sample of benign

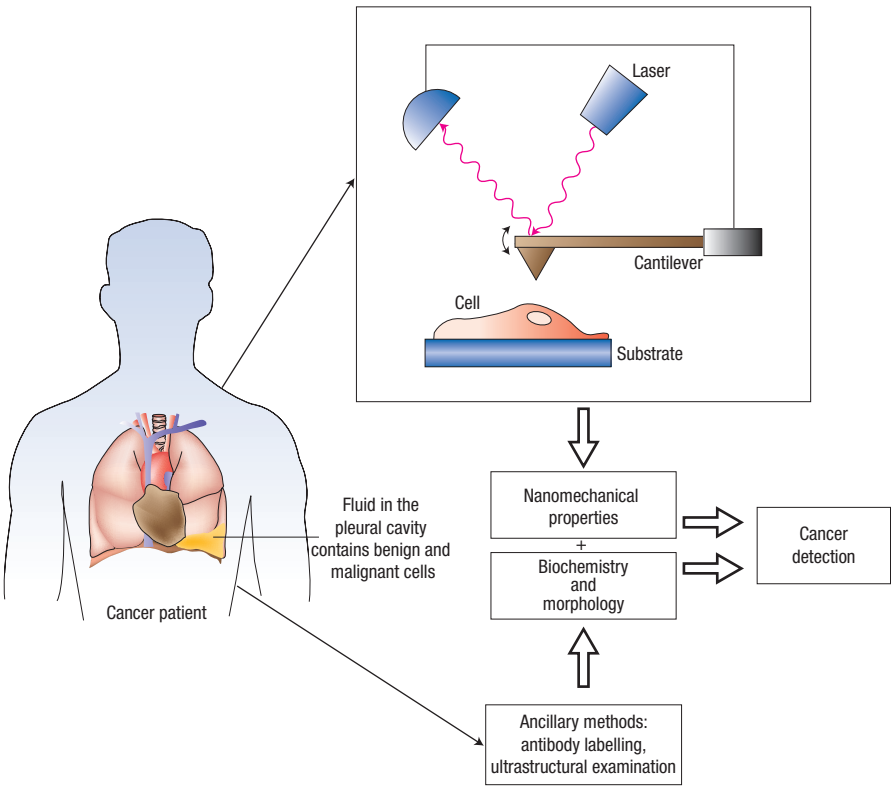

Figure 1 Detecting cancer by probing the elastic properties of cells outside the body. The elasticity of benign cells and malignant cancer cells from patients with suspected metastatic cancer were mechanically probed with an atomic force microscope (top path). The elastic stiffness of the cells was used to distinguish cancerous cells from normal ones. Ancillary methods (bottom path), including various labelling and ultrastructural techniques, confirmed the outcomes of the mechanical analysis. Samples were obtained from cavities in the lung, chest and abdomen.

cells to compare with the population of metastatic cancer cells. Gimzewski and co-workers[9] circumvent these problems by analysing fluid samples taken from the cavities surrounding the lung, chest and the abdomen of patients with suspected metastatic cancer (Fig 1). Because each body fluid sample contains both normal and cancerous cells, the mechanical characteristics could be directly compared.

The elastic modulus — which determines how the cell responds when a force is applied — of the normal and cancerous cells is determined by deforming the cell surface with a sharp probe located at the end of an AFM cantilever (Fig 1). The deflection of the cantilever tip is detected and the elastic stiffness of the cell is estimated from the applied force. Different clinical samples from the human subjects clearly reveal that normal cells from the body fluids were nearly four times stiffer than the cancer cells, as indicated by the higher elastic modulus. The elastic moduli for the benign cells exhibit a wider variation with a log-normal distribution, whereas the malignant cells display a much narrower normal distribution of elastic stiffness.

Interestingly, although vast differences existed in the clinical histories of the patients studied and in the fluid samples and the tumour types, the populations of different metastatic cancer cells showed a common stiffness. The differences in the elastic moduli values of the normal and cancerous cells were statistically significant so healthy and diseased states could be clearly identified, and immunohistological experiments using antibody labels to mark cancerous cells confirmed that the mechanical signature obtained with the AFM was reliable. Moreover, when cells that looked alike were examined, cancerous cells could be singled out by virtue of the difference in mechanical stiffness.

This nanomechanical approach provides a potentially powerful means for detecting cancer along with the other ancillary biomarkers currently used for diagnosis. The results using body fluids from cancer patients are fully consistent with independent *in vitro* biomechanical assays of tumour cells from the human pancreas and breast[6–8]. This strongly suggests that when normal cells transform to cancerous cells, they become less stiff and this correlates with their increased ability to spread more efficiently[4–6].

The current work examines the mechanical response of only a portion of the cell. It is possible to obtain different trends on the elasticity of benign and malignant cells by probing different subcellular components under different stress states, force and displacement ranges, cell culture and substrate conditions, and loading rates[5,8] using a similar nanomechanical approach. However, before this technique can be used as a biomarker for cancer detection, more *ex vivo* studies that sample the mechanical properties of whole cells for a variety of other cancer types are necessary. Furthermore, the influence of other existing diseases on the mechanical properties of normal and cancerous cells should be carefully ruled out before this method can be reliably used in the clinic.

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References

1. Wang, H.-B. Dembo, M. & Wang, Y.-L. *Am. J. Physiol. Cell Physiol.* **279,** C1345–C1350 (2000).
2. Paszek, M. J. *et al. Cancer Cell* **8,** 241–254 (2005).
3. Discher, D., Janmey, P. & Wang, Y.-L. *Science* **310,** 1139–1143 (2005).
4. Bhadriraju, K. & Hansen, L. K. *Exp. Cell Res.* **278,** 92–100 (2002).
5. Bao, G. & Suresh, S. *Nature Mater.* **2,** 715–725 (2003).
6. Suresh, S. *et al. Acta Biomater.* **1,** 15–30 (2005).
7. Guck, J. *et al. Biophys. J.* **88,** 3689–3698 (2005).
8. Suresh, S. *Acta Biomater.* **3,** 413–438 (2007).
9. Cross, S. E., Jin, Y.-S., Rao, J. Y. & Gimewski, J. K. *Nature Nanotech.* advance online publication, 2 December 2007 (doi:10.1038/nnano.2007.397).