EDITORS' CHOICE

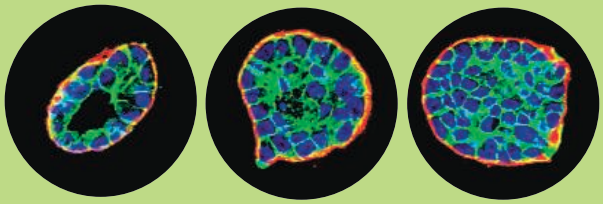
edited by Gilbert Chin

CELL BIOLOGY

A ROCK, a Tumor Cell, and a Hard Place

Tumors are generally stiffer than surrounding healthy tissue, a characteristic that has been exploited in certain diagnostic procedures such as breast self-examination. Tumor rigidity reflects not only intrinsic properties of the tumor cells but also an increased stiffness of the extracellular matrix (ECM). Whether ECM stiffening plays an active role in tumor cell growth or is an innocent bystander has been unclear.

Paszek *et al.* investigated this question by monitoring the behavior of human mammary epithelial cells cultured with ECM components that had been cross-linked to polyacrylamide gels of varying stiffness. These experiments revealed that even a small increase in matrix rigidity enhanced epithelial cell growth. Mechanistically, this effect was traced to a mechano-regulatory circuit that links physical cues from the matrix to transmembrane ECM receptors (integrins), to intracellular regulators of cell contractility such as ROCK (Rho-associated protein kinase), and to a key signaling pathway for cell growth, the mitogen-activated protein kinase pathway. These results suggest that factors causing a sustained increase in matrix stiffness—for example, a chronic inflammatory response—may promote malignant transformation. — PAK



Cell growth with increasing stiffness.

Cancer Cell, in press.

MEDICINE

New Routes to Drugs

Twentieth-century dogma was that drug development for neglected diseases is neglected because there is not enough (or no) profit to be made from the generally impoverished populations who suffer these infections. A recent analysis by Moran reveals a more optimistic turn of events for this century with the burgeoning of public-private partnerships (PPPs), such as the Medicines for Malaria Venture, the Drugs for Neglected Diseases Initiative, and the TB Alliance. PPPs are becoming pivotal in coordinating the efforts of Western multinational pharmaceutical firms, with a range of contacts and clinical experience in academia, with the efforts of smaller biotech and developing-country firms. Moran points out that multinationals are not motivated solely by profit; they also want to burnish their reputations and gain strategic access to developing-country markets and labor skills. By integrating and screening projects and expertise, PPPs synergistically reduce drug development costs from about $1 billion for a Western market to tens of millions for a neglected disease. The good news is that the PPPs will get better and more efficient as their experience grows. — CA

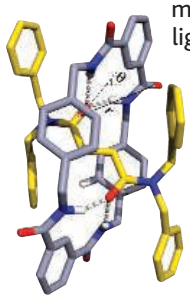
PLoS Med. **2**, e302 (2005).

CHEMISTRY

Fast Vibrational Coupling

Multipulse nuclear magnetic resonance (NMR) spectroscopy is useful for determining the conformations of proteins and other large molecules in solution, but its temporal resolution is limited to microseconds. Recently synthesized nanoscale switches and motors operate on a picosecond time scale, and so require a faster method to gauge their operation. In principle, two-dimensional infrared (2D IR) spectroscopy offers the necessary increase in resolution because it measures coupling between atomic vibrations, rather than nuclear spins.

Larsen *et al.* have taken the preliminary step of showing that a 2D IR pulse sequence effectively reveals the static structure of a rotaxane in solution. This common molecular switch motif consists of a macrocycle that is suspended on an axle via hydrogen bonding; elaborations of this basic structure allow the ring to move when light, current, or chemical reagents are applied. The spectroscopic study quantified coupling between vibrating carbonyl (C=O) groups on the ring and those on the shaft. Analysis of the data through modeling yielded the distance (r = 6.9 Å) and angle (θ = 48°) between these groups, opening the door to a real-time dynamics study of switch and motor operations. — JSY



The rotaxane with the carbonyl oxygens in red.

Proc. Natl. Acad. Sci. U.S.A. 10.1073/pnas.0505313102 (2005).

APPLIED PHYSICS

Highly Heat-Sensitive

The most severe tests of calorimetry are surface processes, where the small number of reaction, binding, or adsorption events limits the amount of heat available for measurement. Fon *et al.* have constructed a cryogenic suspended SiN calorimeter that has a heat capacity resolution of 0.5 attojoule per Kelvin, compared with a typical state-of-the-art resolution of 1 femtojoule per Kelvin. The fast response of interdigitated AuGe resistance thermometers allows sampling every few microseconds, so that temperature changes can be followed via the fast relaxation of the calorimeter. The authors measured the enthalpy change associated with adsorbing 0.16 monolayers of ^{4}He on a device area of 1.2×10^{-9} m^2. The measured value at 2 K corresponds to a heat capacity of 1.4 k_B per helium atom, which agrees well with the measured value for He adsorbed on Grafoil. — PDS

Nano Lett. 10.1021/nl051345o (2005).

BIOCHEMISTRY

A Frozen Giant

Mimivirus (so-named because when subjected to Gram staining it, resembles or mimics a microbe) was first identified a decade ago as a virus growing within amoebae during an outbreak of pneumonia. Since then, its genome has been sequenced

CONTINUED ON PAGE 1969

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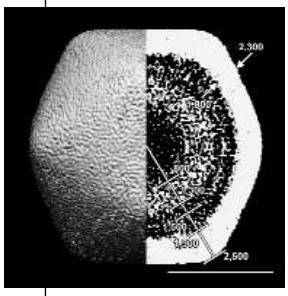
and, at 1.2 Mb, shown to be larger than the genomes of some bacteria and to contain more than 1000 open reading frames (potential protein-encoding genes).

Using cryoelectron microscopy, Xiao *et al.* report that the outer protein shell of the virus is about 5000 Å in diameter and supports a dense mesh of 1250 Å–long fibers that may be collagen triple helices. Inside the capsid are two lipid membranes that surround the supersized genome. A three-dimensional reconstruction to 75 Å resolution is consistent with icosahedral symmetry and an impressively high triangulation number of 1179, indicative of a remarkably accurate assembly of protein subunits into the capsid. — GJC



Reconstructed mimivirus showing the surface and a cross section with dimensions in Å; scale bar, 2000 Å.

J. Mol. Biol. 10.1016/j.jmb.2005.08.060 (2005).

CHEMISTRY

Isomer Identification

Although mass spectrometry is among the most sensitive methods used to identify molecules, it is ill-suited for distinguishing structural isomers, which are chemically distinct entities that have the same mass. Gas or liquid chromatography can be used to separate isomers before applying mass spectrometry, but this adds a relatively slow step.

In traditional mass spectrometry, analytes are ionized nonselectively by collisions with electron or atom beams, and the resulting ions are identified as a pattern of fragments on the basis of their mass-to-charge ratios in electric or magnetic fields. Dela Cruz *et al.* instead use phase-modulated ultrashort laser pulses to induce ionization. By first dispersing the pulses through a tunable liquid crystal array, they introduce wavelength-dependent phase shifts that subtly influence the excited state dynamics of the irradiated molecules. Through trial and error, they determine reproducible pulse shapes that induce different fragmentation patterns in different isomers. One well-shaped pulse, for example, causes *p*-xylene to break into methyl and tropylium fragments more than twice as efficiently as *o*-xylene. Once the pulse shape is determined, it can be used to quantify isomer mixtures in less than a second. Similar pulses were achieved for quantifying mixtures of isomers of cresol and nitrotoluene, and of several cis and trans olefin isomers. — JSY

J. Phys. Chem. A 10.1021/jp0539425 (2005).

HIGHLIGHTED IN *SCIENCE*'S SIGNAL TRANSDUCTION KNOWLEDGE ENVIRONMENT

Science's stke www.stke.org

A Mitochondrial Antivirus Defense

Intracellular viral double-stranded RNA (dsRNA) is detected by the protein RIG-1, which has a C-terminal domain that binds dsRNA. RIG-1 stimulates the coordinated activation of multiple transcription factors, including NF-κB, IRF3, and ATF2, which together act to regulate the expression of type 1 interferons, such as interferon-β (IFN–β), and thus promote the response to viral infection. Seth *et al.* have investigated the role of a protein named MAVS (for mitochondrial antiviral signaling) in mediating the downstream effects of RIG-1. Overexpression of MAVS in HEK293 cells activated IRF-3, NF-κB, and JNK (which activates ATF-2) and increased the abundance of endogenous IFN-β. Silencing MAVS abolished expression of IFN-β in response to Sendai virus. Moreover, MAVS overexpression protected cells from vesicular stomatitis virus–mediated death, whereas MAVS silencing sensitized the cells. Confocal microscopy and subcellular fractionation indicated that MAVS localized to the mitochondria, and localization depended on the transmembrane domain: Replacing this sequence with analogous domains from mitochondrial membrane proteins (Bcl-xL or Bcl-2) preserved MAVS activity, whereas targeting to other membranes reduced it. Thus, MAVS provides an unexpected link between mitochondria and the immune response. Two other groups, Xu *et al.* and Kawai *et al.*, have identified this same protein as an adapter that acts downstream of RIG-1 to stimulate IFN-β expression. — EMA

Cell **122**, 669 (2005); *Mol. Cell.* 10.1016/j.molcel.2005.08.014 (2005); *Nat. Immunol.* 10.1038/ni1243 (2005).

CREDITS: XIAO *ET AL.*, *J. MOL. BIOL.* 10.1016/*J.JMB*.2005.08.060 (2005)

A Frozen Giant

Science **309** (5743), 1967-1969.
DOI: 10.1126/science.309.5743.1967e