October 19, 2010 | vol. 107 | no. 42 | 17853–18232

In This Issue

PNAS
Proceedings of the National Academy of Sciences of the United States of America www.pnas.org

Overeating drives gain differently in upper- and lower-body fat

Previous research has suggested that upper-body fat gain can lead to complications of obesity whereas lower-body fat gain can protect against them. To test whether different body fat deposits grow differently, Yourka Tchoukalova et al. (pp. 18226–18231) recruited 28 healthy, adult volunteers and studied the effect of 8 weeks of overeating on the size and number of fat cells from the volunteers' upper- and lower-body s.c. fat deposits. After overeating, the volunteers gained about 2 kg of upper-body fat and about 1.5 kg of lower-body fat, the authors found. On average, the size but not the number of abdominal, or upper-body, fat cells increased after overeating, the authors report. In contrast, the average number but not the size, of femoral, or thigh, fat cells increased upon overeating. Abdominal fat-cell precursors showed higher levels of RNA messages for proteins involved in fat synthesis than femoral fat-cell precursors, although the authors found no important differences in the replication or cell death rates of the two cell types. Because lower-body fat gain is inversely tied to upper-body fat cell size, the findings provide a potential explanation for the purported beneficial effects of thigh fat, according to the authors. — P.N.

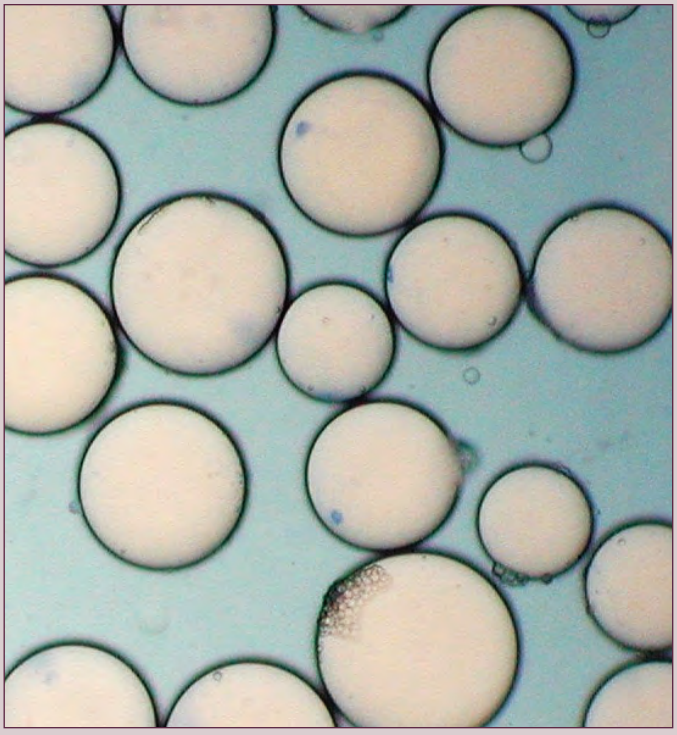
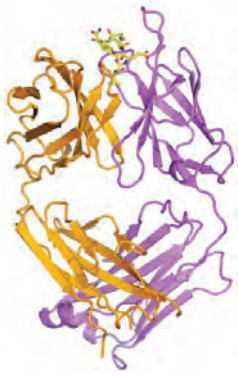


Image courtesy of Michael D. Jensen (Mayo Clinic College of Medicine).

Human fat cells.

Structure-specific antibodies using epitope scaffolds

Epitopes, or the antigenic portions of vaccines that trigger an immune response, often fail to elicit appropriate antibodies when they change shape, hampering the design of vaccines. Gilad Ofek et al. (pp. 17880–17887) used a computational design technique to graft an epitope of the envelope glycoprotein of HIV-1 onto protein scaffolds engineered for optimal structural stability and epitope exposure. The epitope is recognized by the HIV-1 neutralizing antibody 2F5, which has previously shown some promise in clinical trials of HIV prevention. Whereas the freestanding 2F5 epitope generally assumes a helical shape, the antibody-bound epitope adopts a kinked, extended shape. The authors immunized guinea pigs with the epitope scaffolds, which were designed to present the extended shape, and found that some of the epitopes triggered an immune response that closely mimicked that of 2F5. By using X-ray crystallography, the authors also demonstrated that monoclonal antibodies triggered by some of the scaffolded epitopes attached to an HIV-1 peptide fragment and induced the fragment to adopt the shape recognized by the 2F5 antibody. The findings could help improve the design of vaccines based on epitopes that change shape, according to the authors. — P.N.

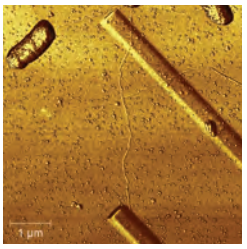


Structure of an epitope-scaffold elicited antibody.

Conductivity measurements along bacterial nanowires

Bacterial nanowires are extracellular appendages that may facilitate electron transport between and among diverse species, including the metal-reducing bacteria, *Shewanella oneidensis* MR-1. Although several biological assays have provided results consistent with bacterial nanowire conductivity, until now researchers had not found direct evidence of electron transport along nanowires. Mohamed El-Naggar et al. (pp. 18127–18131) used nanofabricated electrodes and conducting probe atomic force microscopy

to measure electron transport along individual *S. oneidensis* MR-1 nanowires. The researchers found that the bacterial nanowires were electrically conductive along micron length scales, and estimate that the nanowires' current capacity is sufficient to discharge the cell's respiratory electrons to terminal electron receptors during extracellular electron transport. Bacterial mutants deficient in genes necessary for electron transport produced appendages that were morphologically consistent with wild type nanowires, but were nonconductive. The study suggests that bacteria, the oldest organisms on the planet, may use integrated circuitry for energy distribution, a hypothesis that challenges traditional understanding of extracellular electron transport in microbial communities, according to the authors. — J.M.



Extracellular appendages interrogated by nanofabricated electrodes.

Pleiotropy favors the evolution of complexity

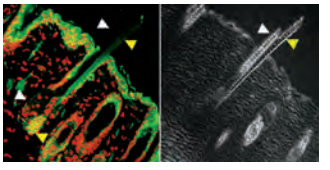
The ability of one gene to affect multiple phenotypic traits is a well established phenomenon known as pleiotropy. Researchers have developed mathematical models to theoretically examine the phenomenon's biological implications; however, few studies have analyzed the impact of pleiotropy by using empirical methods. Jianzhi Zhang et al. (pp. 18034–18039) compiled phenotypes of yeast, nematode, and mouse mutants from previous studies and databases, and mathematically characterized the organisms' genomic patterns of pleiotropy. The patterns, the authors report, reveal unexpected gene–trait relationships that contradict current theory about the role of pleiotropy in evolution. Evolutionary biologists have based theories on the assumption that all genes affect all traits and that the total effect of a gene on all traits is identical. According to the authors, however, their analysis indicates that for most genes, the fraction of traits that are affected by deleting the gene is minute. In addition, genes that are associated with greater numbers of traits exhibit a greater effect per trait. Taken together, the findings suggest that pleiotropy promotes the evolution of complexity in organisms, in contrast to the more widely held belief that complexity slows adaptation rates. The authors propose that past inferences derived from theoretical models of pleiotropy may need to be reevaluated. — T.J.

3D imaging tracks single mRNA particles in cells

mRNA and protein complexes regulate gene expression at the molecular level. While much has been learned about mRNA transport in 2D by standard microscopy, little is known about the 3D dynamics of RNA message transport and interactions with other biomolecules—information that would lead to a better understanding of the spatial and temporal control of gene expression as well as key cellular processes. Michael Thompson et al. (pp. 17864–17871) employed a microscope with a double-helix point spread function (DH-PSF) and statistical methodology to track single mRNA-protein complexes in 3D in live budding yeast cells. DH-PSF microscopy converts the normal single fluorescence spot from an emitter-tagged biomolecule into two spots. Different positions along the z-axis are sensed by the imaging system as different angles between the two spots—carving out a "double-helix" along the z axis. With the DH-PSF, the researchers followed the fate of *ARG3* mRNA, which encodes a housekeeping enzyme involved in amino acid biosynthesis. By modifying two mathematical models used to assess movement in 2D, namely speed correlation and confinement indices, the authors quantified both the confined, Brownian, and directed motion of *ARG3* mRNA-protein complexes at 25-nm precision in the x and y dimensions and 50-nm precision in the z dimension. The authors demonstrated that for this mRNA, a small proportion appear to move nonrandomly, including periods in which the mRNA appears stationary, confined, and directed in its motion. — F.A.

Long-distance effects of localized tumors

Researchers have established that nonspreading tumors can affect neighboring noncancerous cells by inducing inflammation and DNA damage in the tissues surrounding the tumors. But the remote effects of localized tumors on the health of distant tissues are poorly understood. To determine whether the mere presence of a tumor has widespread effects on an animal's health, Christophe Redon et al. (pp. 17992–17997) subcutaneously implanted nonspreading melanoma, sarcoma, or carcinoma cells in mice and measured the levels of DNA damage and inflammation in distant tissues by using established indicators. Compared to controls, the mice with the implanted tumors showed higher levels of DNA damage, including double-strand breaks and clustered DNA lesions, in the skin and gastrointestinal (GI) tract, the authors report. The tumor-bearing mice also showed signs of inflammation in faraway sites, indicated by activated macrophages in the GI tract and by a spike in the level of the cytokine CCL2 in the blood serum. However, tumors implanted in engineered mice lacking CCL2 failed to produce high levels of DNA damage in distant sites, suggesting that the cytokine is crucial to the onset of damage. The findings suggest that early stage localized tumors may have more widespread and serious effects on an animal's health than documented thus far, according to the authors. — P.N.



Hair follicles in stages of their life cycle.