March 10, 2009 | vol. 106 | no. 10 | 3641–4062

PNAS

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

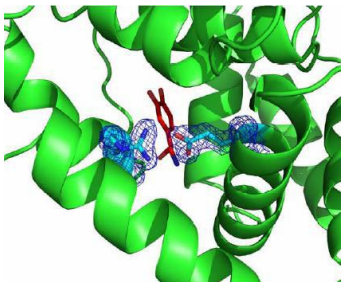
In This Issue

3728 Multifunctional mosquito salivary protein
3770 Sequence context-specific searching
3847 Neural correlates of beauty appreciation differ by gender
3913 Noninvasive biomarker detects advanced breast cancer
3970 Magnetic sweep for cancer

BIOCHEMISTRY

Multifunctional mosquito salivary protein

As a female mosquito begins its blood meal, the release of biogenic amines and eicosanoids from host mast cells rapidly follows the onset of feeding. Mosquito saliva contains a variety of proteins to counteract the host immune response, such as the D7 family that neutralizes the small molecule effectors of inflammation. Eric Calvo et al. describe the detailed structure and bifunctionality of the 2-domained D7 protein from the saliva of *Aedes aegypti* (AeD7). Previous studies had found that only the C-terminal domain of AeD7 was homologous to other D7 proteins, suggesting that the N-terminal had a yet-undetermined function. The authors used isothermal titration calorimetry and ligand complex crystal structures to show that the N-terminal domain of AeD7 bound the lipid chain of cysteinyl leukotrienes in a hydrophobic pocket. The C-terminal domain, the authors found, bound biogenic amines in a manner similar to other single domain D7 proteins. Binding of norepinephrine in the C-terminal led to a shape change in the protein that created an ordered α-helix and buried the active site. The bifunctionality of the AeD7 protein underscores the importance of interrupting the host's inflammatory response, the authors conclude. — C.A.



AeD7 changes shape upon binding of norepinephrine.

"Multifunctionality and mechanism of ligand binding in a mosquito antiinflammatory protein" by Eric Calvo, Ben J. Mans, José M. C. Ribeiro, and John F. Andersen (see pages 3728–3733)

BIOPHYSICS AND COMPUTATIONAL BIOLOGY

Sequence context-specific searching

The sequence homology of a protein can give clues to its function, because closely related proteins frequently perform similar tasks in an organism. However, a simple comparison of amino acid sequences does not necessarily account for local sequence context and may not yield accurate results. Andreas Biegert and Johannes Söding generated a library of sequence profiles that represent all short subsequences in the nucleotide and protein sequence databases. With this library, the authors assigned amino acid similarities depending on neighboring residues, yielding more sensitive results than traditional BLAST searches at the same speed. The new context-specific BLAST (CS-BLAST) uses context-specific pseudocounts to generate a profile from the query sequence, and then uses the profile-to-sequence search function of BLAST. Rather than relying on 3D structural information, context-dependent methods determine the local environment of a residue by identifying the surrounding residues and can help to predict into what amino acids a specific residue is likely to mutate. Sequence context-specific comparisons offer similar benefits for aligning nucleotide sequences, according to the authors. — C.A.

"Sequence context-specific profiles for homology searching" by A. Biegert and J. Söding (see pages 3770–3775)

EVOLUTION, PSYCHOLOGY

Neural correlates of beauty appreciation differ by gender

Behavioral studies have shown that men and women assess the beauty of visual scenes and decorated objects in different ways. Previous analyses have confirmed variations in neural activity by gender in the brain during spatial processing tasks. Activated regions in the female brain are symmetrically distributed, whereas the male brain utilizes the right hemisphere more strongly than the left. Camilo Cela-Conde et al. find there may be a link between the brain's spatial processing and perception of beauty; the authors suggest that differences in the neural

Gender difference in aesthetic preferences may have begun with human hunter-gatherers. Photograph by Camilo J. Cela-Conde.

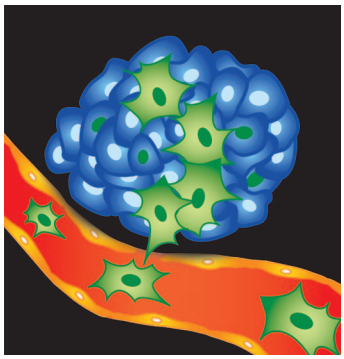
correlates of beauty appreciation appear very similar to those for spatial processing. The authors used magnetoencephalography to examine the activity in the cortex of male and female subjects who were shown paintings and urban scenes and asked to rate them as "beautiful" or "not beautiful." Activity was highest in the parietal lobe and peaked in the period 300–900 ms after images were shown. The delay suggests that the activity is not related to immediate perception but to judgement. Male brains were active only in the right hemisphere, female brains in both. Because the parietal lobe has evolved greatly since human and chimpanzee lineages diverged, the gender disparity in neural correlates of beauty likely postdates the split, the authors say. — K.M.

"Sex-related similarities and differences in the neural correlates of beauty" by Camilo J. Cela-Conde, Francisco J. Ayala, Enric Munar, Fernando Maestú, Marcos Nadal, Miguel A. Capó, David del Río, Juan J. López-Ibor, Tomás Ortiz, Claudio Mirasso, and Gisèle Marty (see pages 3847–3852)

MEDICAL SCIENCES

Noninvasive biomarker detects advanced breast cancer

As one of the most common forms of cancer, breast cancer kills more than half a million people worldwide each year. Jiang Yang et al. identified a small extracellular protein called lipocalin 2 (Lcn2) that promotes the progression of the disease and may potentially be used to detect advanced breast cancer. In cells, lipocalins typically transport and present lipids and other small hydrophobic molecules to cell-surface receptors, thereby playing a role in cell activities such as regulation, proliferation, and differentiation. The authors studied human tissue and urine samples and found that elevated Lcn2 levels were consistently associated with invasive breast cancer. In breast cancer cells, over-expressed Lcn2 upregulated mesenchymal cell markers, including proteins vimentin and fibronectin. Lcn2 also downregulated the epithelial marker E-cadherin, reduced the expression of estrogen receptor α, and increased cell motility and invasiveness. The transition from epithelial to mesenchymal cells is a key process associated with metastasis, as is a reduced response to the hormone estrogen in breast cancer. In mice, breast tumors expressing lipocalin displayed a poorly differentiated phenotype and showed an increase in local tumor invasion and lymph node metastasis. This work may help in the development of therapeutics to treat breast cancer and contribute to detection efforts, the authors say. — F.A.



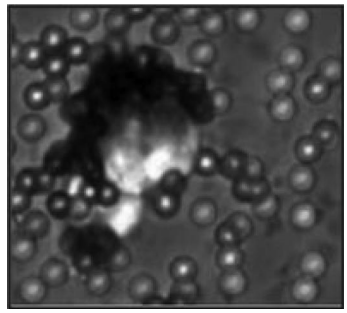
Lipocalin 2 induces mesenchymal transition.

"Lipocalin 2 promotes breast cancer progression" by Jiang Yang, Diane R. Bielenberg, Scott J. Rodig, Robert Doiron, Matthew C. Clifton, Andrew L. Kung, Roland K. Strong, David Zurakowski, and Marsha A. Moses (see pages 3913–3918)

MEDICAL SCIENCES

Magnetic sweep for cancer

The presence of a metastatic tumor is evidenced by rare circulating epithelial cells in a patient's blood. But current technology to identify these cells is not efficient, which makes it difficult for physicians to predict the course of tumor development. Immunomagnetic separation, the leading technology, is able to enrich a final sample to ≈0.1% epithelial cells. In this technique, antibodies to epithelial cell markers are linked to magnetic beads; cells are labeled with the antibodies and extracted by powerful magnets. AmirAli Talasaz et al. present a versatile version of immunomagnetic isolation—dubbed "MagSweeper"—that can achieve greater isolation efficiency than current methods. MagSweeper consists of an array of rod-shaped neodymium magnets wherein each magnet is encased in a thin plastic sleeve, which makes it possible to withdraw the magnets and release captured cells. A user is then able to identify individual epithelial cells visually and extract them robotically for characterization. Using blood seeded with cancer cells at densities typical of clinical samples, MagSweeper was able to pluck out approximately 60% of the targeted cells with 5% purity. The throughput rate is an order of magnitude greater than that of the current microfluidic techniques, the authors say. — K.M.



MCF7 cells isolated by MagSweeper.

"Isolating highly enriched populations of circulating epithelial cells and other rare cells from blood using a magnetic sweeper device" by AmirAli H. Talasaz, Ashley A. Powell, David E. Huber, James G. Berbee, Kyung-Ho Roh, Wong Yu, Wenzhong Xiao, Mark M. Davis, R. Fabian Pease, Michael N. Mindrinos, Stefanie S. Jeffrey, and Ronald W. Davis (see pages 3970–3975)