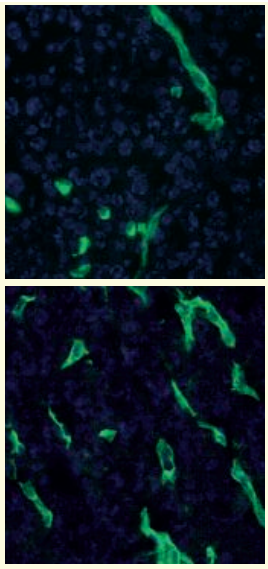
EDITORS' CHOICE

edited by Gilbert Chin

BIOMEDICINE

Resisting Arrest

An exciting class of cancer drugs acts by disrupting the growth of new blood vessels that supply solid tumors with oxygen and other essential nutrients. Because antiangiogenic therapies target genetically stable endothelial cells rather than genetically adaptable tumor cells, it had been hypothesized that tumors would be unlikely to develop resistance to these drugs. However, the results of clinical trials reveal that tumors do in fact eventually escape the growth-inhibitory effects of these drugs, although the underlying mechanisms of resistance have been unclear.



Growth of blood vessels (green) after anti-VEGFR2 (10 days, top; 4 weeks, bottom).

Casanovas *et al.* show that resistance can arise when tumors exploit a redundancy in the signaling pathways that drive angiogenesis; that is, when a drug incapacitates one pathway, tumors are able to reactivate angiogenesis through a second pathway. In a mouse model of pancreatic cancer, blocking vascular endothelial growth factor (VEGF) signaling with an antibody to VEGF receptor 2 (VEGFR2) produced a temporary arrest of tumor angiogenesis and tumor growth. Subsequently, a second wave of angiogenesis, driven by fibroblast growth factors (FGFs), led to resumption of tumor growth. Inhibiting FGF signaling during this second stage effectively blunted tumor recovery from hypoxia, and the authors propose that maximal therapeutic benefit may come from the use of drug combinations that target multiple angiogenic pathways. — PAK

Cancer Cell **8**, 299 (2005).

IMMUNOLOGY

Sharing Control

The transcription factor T-bet, encoded by *Tbx21*, is a critical regulator of T helper cell type 1 differentiation. Nevertheless, in the development of CD8 functions such as cytotoxicity and interferon-γ production, T-bet function appears to overlap with that of a related transcription factor, eomesodermin (Eomes).

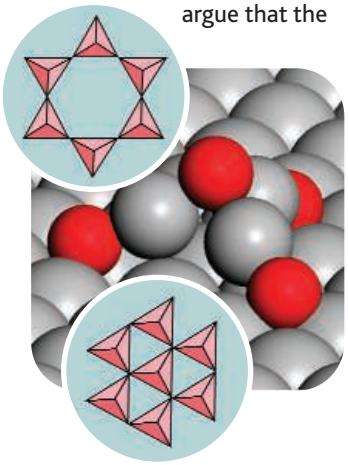
Intlekofer *et al.* explored this relationship by engineering combined genetic deficiencies of the two transcription factors. Because deletion of both *Eomes* alleles results in embryonic lethality, mice carrying heterozygous *Eomes* mutations were crossed with those carrying *Tbx21* mutations. Even with only a partial loss of Eomes, this led to significant diminution in both the number and function of memory $CD8^+$ T cells and natural killer cells, which resembles the phenotype of mice lacking the cytokine interleukin (IL)–15. Furthermore, this correlated with the loss of a marker for IL-15 responsiveness, suggesting a direct coupling of Eomes/T-bet activity with the acquisition of IL-15–directed cellular immune functions, including the long-term renewal of $CD8^+$ memory T cells. —SJS

Nat. Immunol. 10.1038/ni1268 (2005).

SURFACE SCIENCE

An Evolving Oxide Structure

One of the early triumphs of surface science was an explanation for the $p(4\times4)$ diffraction pattern observed when oxygen was adsorbed on the closest packed (111) surface of silver. In the mid-1970s, Rodiva and co-workers noted that the diagonal of the unit cell of the (111) surface of Ag_2O was within 0.3% of being four times the distance between Ag atoms on the (111) surface of the metal. With various modifications (which led to a stoichiometry of $Ag_{1.83}O$ for the overlayer), many other studies, including scanning tunneling microscopy and density functional theory (DFT) calculations, have supported a hexagonal overlayer model. Michaelidis *et al.* review the history of this problem and argue that the basic building block of the overlayer is more likely to be a pyramidal Ag_3O_4 unit. A number of nearly equivalent low-energy structures can be formed that are more stable in DFT calculations than the $Ag_{1.83}O$ model.— PDS



The Ag_3O_4 unit on the Ag substrate (main; Ag, gray; O, red) and several ways in which the pyramids may be arranged (insets).

J. Vac. Sci. Technol. A **23**, 1487 (2005).

ASTROPHYSICS

Cosmic Ringing

Gravitational attraction causes galaxies to clump together ever more strongly over time, creating a cosmic web of filaments, clusters, and superclusters. Tiny density fluctuations in the hot early universe, including ripples caused by sound waves in the plasma, have been amplified by gravity to produce the galaxy structures we see today. The faint ringing of these sound waves has been picked up in the distribution of the millions of galaxies mapped in the Sloan Digital Sky Survey.

Eisenstein *et al.* measured the correlation function of luminous red galaxies from the survey, finding a strong signal corresponding to structures with sizes of 100 Mpc, typical of superclusters of galaxies. This scale is as predicted from theories of structure in the cosmic microwave background, linking the physics of sound waves in the early universe to galaxy distributions. Eisenstein *et al.* use this correspondence to measure the overall density of matter in the universe (30%) and to infer the presence of dark energy. — JB

Astrophys. J. **633**, 560 (2005).

BIOCHEMISTRY

Pattern Recognition

Protein-protein interaction space is gradually becoming less nebulous as predictions from global two-hybrid screens of model organisms are confirmed or refuted on the basis

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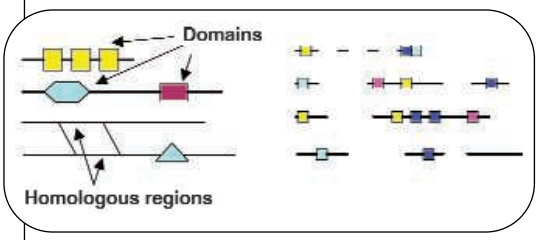
of direct experimental trials or structure- and sequence-based bioinformatic analyses. On the other hand, lower-affinity interactions between smaller, peptide-sized linear motifs and their protein partners have been more difficult to catalog, in part because they are more likely to be found in the disordered (nonhelical, nonsheet) regions of protein structures and because they may be less conserved across species.

Neduva *et al.* propose a bioinformatic approach for identifying these short stretches of amino acids and apply it first to a curated set of eukaryotic linear motifs and then to the two-hybrid data set from *Drosophila*. From the sequences of a group of predicted partner proteins, they remove well-defined structural elements and homologous regions. By assessing the nonrandom appearance of peptide motifs in what remains, they obtain rankings of candidates; two of their predictions, tested in binding assays, are peptides with affinities of 20 and 40 μM, suggesting that it might now be possible to look at weak or transient interactions in a systematic fashion (see also Ruotolo *et al.*, Reports, *Science* Express, 17 November 2005). — GJC

PloS Biol. **3**, e405 (2005).



Removing domains and homologous regions (left, shapes) to uncover similar linear motifs (right, squares).

CREDIT: NEDUVA *ET AL.*, *PLOS BIOL.* 3, E405 (2005)

CHEMICAL ENGINEERING

A Hot Spot of Activity

The kinetics of heat flow during chemical reactions usually becomes a concern only for large-scale industrial manufacturing. However, Hyde *et al.* show that even during small-scale studies in the laboratory, local heating can lead to surprising results. Previously, the authors had found that attempts to reduce vinyl cyclohexene by palladium-catalyzed hydrogenation in supercritical carbon dioxide yielded instead a dehydrogenated product, ethyl benzene. To explore this puzzling observation, they monitored reactivity in the absence of H_2 by gas chromatography/mass spectrometry, analyzing the data using two-dimensional correlation techniques. The results suggested that an initial burst of hydrogenation generates intense heat locally, which degrades the catalyst and ignites the self-sustaining and exothermic dehydrogenation process. Thermocouple measurements confirmed that H_2 addition produces hot spots of 200°C in a catalyst column that is otherwise near room temperature. — JSY

Angew. Chem. Int. Ed. 10.1002/anie.200502049 (2005).

HIGHLIGHTED IN *SCIENCE*'S SIGNAL TRANSDUCTION KNOWLEDGE ENVIRONMENT

Science's stke www.stke.org

Linking Oxygen to Differentiation

Cells can detect an insufficiency of oxygen and activate signaling pathways that decrease metabolic oxidative phosphorylation or increase proliferation of blood vessels. Hypoxia also causes various stem or progenitor cells to remain in an undifferentiated state. Gustafsson *et al.* show that this latter response to hypoxia is mediated by an interaction between the oxygen-sensing mechanisms of the cell with the Notch signaling pathway. Cells use prolyl hydroxylases to sense oxygen, and these enzymes control gene expression via the transcription factor hypoxia-inducible factor-1α (HIF-1α). The membrane protein Notch can undergo proteolytic cleavage, which allows its intracellular domain (ICD) to move into the nucleus and to interact with other proteins to regulate expression. The effects of hypoxia on differentiation of cultured mouse muscle precursor cells or primary rat neural stem cells depend on Notch signaling and were prevented by an inhibitor of the protease that generates the Notch ICD. The authors propose that HIF-1α may interact with the Notch ICD and showed that they do so in vitro. Furthermore, chromatin immunoprecipitation analyses showed that HIF-1α is recruited to the promoter regions of Notch-responsive genes in cells exposed to hypoxia, provided that Notch signaling was also activated. These results help explain the mechanisms that couple oxygen sensing to control of differentiation.— LBR

Dev. Cell **9**, 617 (2005).

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A Hot Spot of Activity

Science **310** (5751), 1093.
DOI: 10.1126/science.310.5751.1093a