

BIOMEDICINE

Solid Tumors in Living Color

The behavior of tumors is profoundly influenced by the microenvironment in which they grow. In addition to diffusible extracellular factors, this environment harbors a complex and dynamic population of stromal cells, including fibroblasts and a variety of immune cells. Because different types of stromal cells can have opposing effects on tumor progression and responses to therapy, it is important to understand how each cell type behaves in actively growing tumors.

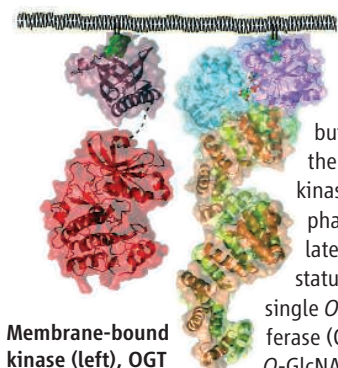
Egeblad *et al.* have combined confocal microscopy with multicolor imaging techniques to record in living mice the movement and localization patterns of tumor-infiltrating stromal cells during a 12-hour period. One feature shared by several stromal cell types was greater motility at the tumor periphery than within the tumor mass. Regulatory T cells were found to migrate near blood vessels, and their movement was sensitive to tumor oxygen levels; in contrast, the movement of myeloid cells (the most heterogeneous group of stromal cells) was insensitive to oxygen, and their localization patterns and migration rates varied according to cell-surface marker expression, probably reflecting important functional differences. By helping to define the contributions of specific stromal cells to tumor growth, this imaging technology may lead to more effective therapies. — PAK

Disease Models Mech. **1**, 155 (2008).

BIOCHEMISTRY

A Pinch of Sugar

In metazoans, many cellular proteins are regulated by posttranslational modification of serine and threonine residues with *N*-acetylglucosamine to create an *O*-GlcNAc appendage.



Membrane-bound kinase (left), OGT (right).

Acylation may compete for the same residues as phosphorylation, but in contrast to the hundreds of kinases and phosphatases that regulate phosphorylation status, there is but a single *O*-GlcNAc transferase (OGT) and a single *O*-GlcNAc hydrolase.

Because no acylation sequence motif has been identified as yet, how OGT recognizes its protein substrates remains unclear.

PHYSIOLOGY

Not Fat, Just Well Covered

Adélie penguins breed on the Antarctic ice, and the chicks, to survive, must rapidly establish a layer of fat to protect themselves against the sub-zero temperatures and to enable them to enter the water a mere 2 months after hatching. Raccurt *et al.* investigated the transcriptional program responsible for this speedy production of adipose tissue by taking autopsy samples from the chicks of 16 out of the 34,000 penguin pairs that breed on the Pointe Geologie archipelago. They then measured the expression levels of transcription



factors, hormone receptors, and other genes known from *in vitro* studies of mouse and chicken cells to be involved in the growth and differentiation of adipocytes. In the first 2 weeks, while a chick was at least partially protected by sheltering in a parent's brood pouch, growth hormone and 3,5,3'-triiodo-thyronine (T_3) receptors along with the transcription factor GATA3 marked a period of intensive adipocyte differentiation and development. After day 15, when chicks had outgrown their brood pouches, lipoprotein lipase, PPAR γ , and other factors associated with adipocyte maturation and lipid storage took over to produce large fat-filled cells that formed a thermally insulating layer. This is similar to the changes seen in chicken cells, but subtle differences demonstrate how in penguins that pattern is tailored to their particular habitat. — CS*

Am. J. Physiol. Regul. Integr. Comp. Physiol. **295**, 10.1152/ajpregu.90371.2008 (2008).

Clarke *et al.* report the structure of OGT both in the apo state and in complex with a phosphonate analog of the sugar donor UDP-GlcNAc. The N-terminal domain comprises repeats of the tetratricopeptide (TPR) protein interaction module and the catalytic C-terminal domain has two subdomains that together form the metal-independent glycosyltransferase fold GT-B. The UDP-GlcNAc analog is pinched between the subdomains at the bottom of a conserved groove that is suitably shaped to bind substrate peptides; the TPRs interact with the catalytic domain so that the putative substrate binding groove extends into the TPR domain. The authors present mutagenesis data

consistent with the proposal that peptides bind in the active-site groove, with proteins binding to the extended surface formed by the TPRs. A phosphoinositide binding site is located on the surface of the catalytic domain and may recruit OGT to membrane-bound targets. — VV

EMBO J. **27**, 10.1038/emboj.2008.186 (2008).

CHEMISTRY

A Jolt from Ethanol

One advantage enzymes tend to have over synthetic catalysts is their capacity as very large molecules to create an environment that fully surrounds a substrate and thereby mediates

efficient reactivity through delocalized polarity effects. A simplified means of probing these reaction medium influences is to vary the solvent in which small-molecule catalysts operate. Liu *et al.* have explored the medium effects in a phosphate diester hydrolysis reaction catalyzed by a di-zinc complex that models enzymes that cleave nucleic acids at backbone sites. They find that although the catalyst is not highly active in aqueous solution, a shift into ethanol solvent results in marked acceleration. Moreover, the catalyst is remarkably selective for hydrolysis over ethanolysis, yielding a nearly 1:1 mixture of the competing products at an ethanol:water ratio exceeding 600:1. Based on comparison with the rate of the uncatalyzed background hydrolysis in ethanol, the authors posit a 10^{17} -fold accelerating effect of the catalyst in this conducive medium. — JSY

J. Am. Chem. Soc. **130**, 13870 (2008).

HYDROLOGY

How Wet Crops Get

One of the major challenges posed by both increasing global population and climate change is the wise use of water. An enormous quantity of fresh water is used in agriculture, and planning in the face of dwindling resources requires an understanding of current and past consumption. With the aid of a global vegetation and water balance model, Rost *et al.*

provide a global assessment of agricultural water use and evaluate how changes in land use affected water consumption during the 20th century. Their analysis shows that although globally agriculture is mostly based on the use of precipitation directly, major agriculture in India, China, Pakistan, and the United States depends

heavily on diversions from rivers or groundwater; about half is from nonrenewable sources. Historically, their analysis implies that the global expansion of agriculture since 1900 probably increased discharge by nearly 5% (despite an increase in withdrawals for irrigation over time), an amount about comparable in some cases to effects from climate change alone. Thus, land-use changes need to be considered in adapting water use to climate change. — BH

Water Resour. Res. **44**, 10.1029/2007WR006331 (2008).



DEVELOPMENT

Flower Power

Some plants, such as the poppy, form a single flower at the tip of the plant; others, such as the petunia or tomato, also flower at the tip but then generate a new lateral meristem that becomes the new tip, and then makes a new flower and a new meristem, yielding a zig-zag pattern of flowers. Rebocho *et al.* have identified a gene in petunia called *EVERGREEN (EVG)*, which is required for formation of the new lateral meristem. Mutants deficient in *EVG* grow normally, but don't zig-zag or flower. *EVG* is expressed in the apical meristem after the plant matures to the point of flowering, where it promotes the expression of *DOUBLETOP (DOT)*, a transcriptional activator that determines flower formation. The function of *EVG* seems to be to support the separation of the new meristem as the previous meristem becomes a flower. Analysis of related genes in *Arabidopsis* suggests that *EVG* may function to control cell proliferation. — PJH

Dev. Cell **15**, 437 (2008).

SIGNAL TRANSDUCTION

Screening for Kinases

Hedgehog (Hh) ligands are regulators of developmental patterning, and overactivity of the Hh signaling pathway is associated with some human cancers. Genetic approaches in *Drosophila* have identified many components of the signaling pathway, but Hh signaling is still incompletely understood, particularly in vertebrates, in which the components of the pathway differ substantially from their counterparts in flies. Evangelista *et al.* searched for protein kinases that influenced Hh signaling by monitoring the effects of a library of siRNA molecules on the expression of a reporter gene in mammalian cells. One kinase identified in the screen was a member of the cyclin-dependent kinase family, Cdc21, which regulates mitosis and apoptosis; Cdc21 directly interacts with Suppressor of Fused (an inhibitor that keeps the Gli transcription factor from

moving to the nucleus and activating Hh-dependent gene transcription). Overexpression of Cdc21 in cultured cells or in zebrafish embryos enhanced Hh signaling. Thus, the authors propose that Cdc21 is a component of the Hh pathway that may have been missed in genetic screens because of the harmful effects of the loss of a multifunctional protein. — LBR

Sci. Signal. **1**, ra7 (2008).

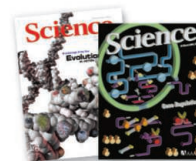
*Chris Surridge is a locum editor in *Science's* editorial department.



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