■ CANCER

Tough tumors

A new report explains how cancers stiffen the extracellular matrix to foster growth and metastasis (*Cell* **139**, 891–906).

Much like normal tissue, tumors initially grow contained within the extracellular matrix (ECM), which provides structural support and communication with the environment. But as they progress, tumors modify the composition and elasticity of the ECM, turning a soft barrier of collagen into a hard surface. It has been unclear how malignant cells orchestrate these changes and how ECM reciprocally affects cancer growth.

Kandice Levental *et al.* measured physical alterations in the mammary gland tissue of mice bearing breast tumors. They observed that activity of a collagen crosslinking enzyme increased as tumors develop, resulting in stiffening of the extracellular matrix.

The researchers next examined collagen remodeling in a tissue culture system that recapitulates ECM properties. Cells grown inside tightly crosslinked collagen formed stronger contacts with their surroundings. These enhanced focal adhesions bumped up the activity of integrins, which fueled malignancy by turning on cell growth pathways in the tumor. In support of this model, inhibition of collagen crosslinking or integrin signaling blocked tumor progression in mice. —*VA*

Ordered chaos

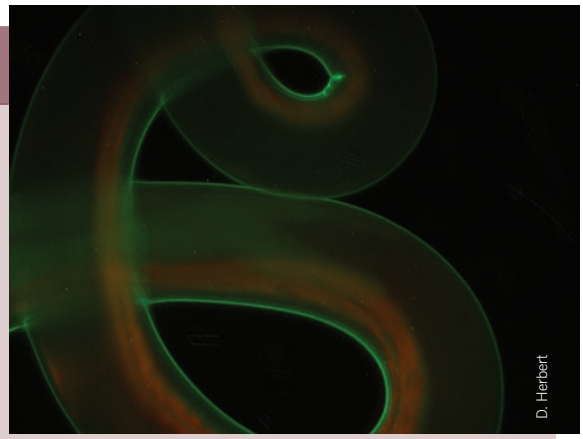
Fifty to seventy percent of prostate tumors contain specific chromosomal translocations that help drive tumorigenesis. Two new studies show that the androgen receptor is to blame.

Androgen signaling promotes the interaction of chromosomal regions containing binding sites for the androgen receptor, report Ram-Shankar Mani *et al.* (*Science* **326**, 1230) and Chunru Lin *et al.* (*Cell* **139**, 1069–1083). Once the DNA regions are in proximity, translocations are fostered by the recruitment of enzymes that promote double-stranded DNA breakage, according to Lin *et al.* They found that prostate cancer cells overexpressed some of these enzymes.

The findings dovetail with previous work suggesting the estrogen receptor could similarly promote translocations by bridging two chromosomal regions. Perhaps translocations arise in other types of tumors through the action of nuclear receptors and DNA-breaking enzymes, speculate the researchers. —*CS*

INFECTIOUS DISEASE

Worms get slimed



A worm that has successfully fed on its host (rhodamine B, red, in alimentary canal). Outer cuticle in green.

The gut can secrete a sticky mucous substance that slimes up gastrointestinal worms, disorients them and causes their expulsion, according to a study in mice.

De'Broski Herbert *et al.* found that such expulsion is initiated by interleukin-4 and interleukin-13, cytokines that are upregulated in response to infection by worms that infect the intestinal lumen, such as *Heligmosomoides polygyrus*. These cytokines, in turn, induce epithelial cells to develop into goblet cells that secrete resistin-like molecule-β (RELM-β). It's this molecule that helps form the mucous layer around the worms, blocking their chemosensory organs and their ability to feed on host tissue (*J. Exp. Med.* 206, 2947-2957; 2009). RELM-β does not, however, seem to expel other worms, such as *Trichinella spiralis*, which resides in the intestinal epithelium. —*MW*

■ IMMUNITY

Two fronts against flu

How much has our exposure to seasonal strains of influenza protected us from H1N1 'swine' flu, an antigenically distinct virus? Previous studies showed that neutralizing antibodies are required for protective immunity, whereas T cell responses can modulate disease severity. New work now shows that people show similar levels of T cell responses to both pandemic and seasonal strains of influenza (*Proc. Natl. Acad. Sci. USA* **106**, 20365–20370; 2009).

Jason Greenbaum *et al.* screened databases of influenza epitopes, portions of viral proteins recognized by the immune system. The authors found a substantial degree of viral immune epitope conservation between pandemic and seasonal influenza, with T cell epitopes showing higher conservation than B cell epitopes (69% versus 31%, respectively). This finding dovetails with previous work showing a low frequency of neutralizing antibodies to swine flu in the general population. Results of the epitope screen were confirmed in peripheral blood mononucleocytes from normal human donors, which showed memory T cell activity against pandemic influenza antigens.

The study elucidates a mechanism behind the pattern of high infectivity and low disease severity shown by the pandemic swine flu. The finding could also aid in the design of vaccines against the most immunogenic regions of the flu. —*AK*

Backup generators

Chemotherapy for acute myeloid leukemia (AML) typically leads to a drastic reduction in lymphocyte numbers, termed lymphocytopenia, yet treated patients rarely develop viral infections. A new report sheds light on this apparent paradox by showing that a subset of memory T cells resists chemotherapy and helps rebuild the immune system after lymphocytopenia (*Immunity*. **31**, 834–844; 2009).

Cameron Turtle *et al.* identified a subset of central memory (T_{CM}) and effector memory (T_{EM}) $CD8^+$ T cells that expel daunorubicin, a cancer drug that kills cells. The ejection occurred through the ABCB1 transporter, which was upregulated on the cells. Further studies showed that these drug-effluxing T cells had been previously exposed to antigen and could proliferate in response to cytokines that act to restore T cell numbers during lymphocytopenia.

Compared to unaffected individuals, subjects with AML with lymphocytopenia had higher counts of actively dividing T_{CM} and T_{EM} cells that effluxed daunorubicin. These cells could self-renew and differentiate into memory cells with lower drug efflux capacity when exposed to antigen in the presence of inflammatory signals—suggesting they might have stem cell–like qualities.

The findings suggest that select memory T cells not only survive chemotherapy but can respond to viral antigens, proliferate and differentiate into other memory subsets—thereby aiding in the reconstitution of $CD8^+$ T cell memory following lymphocytopenia. —*AK*

■ NEUROSCIENCE

Releasing the brake

Nerve injury triggers the release of factors that can both enhance and suppress axon growth. Blocking the inhibitory signals promotes the intrinsic capacity of nerves to regenerate, report Zhigang He and colleagues (*Neuron*, **64**, 617–623; 2009).

Cytokines and growth factors released upon injury promote axon regeneration while simultaneously activating a negative feedback loop mediated by suppressor of cytokine signaling-3 (or SOCS3). Activation of SOCS3 is essential in maintaining control over the magnitude and duration of cytokine action; however, prolonged activation of SOCS can suppress the regenerative capacity of axons.

The researchers found that selective deletion of SOCS3 in the eye promotes extensive optic nerve regeneration up to 1 mm away from the injury site. This effect was mediated by signals downstream of the receptor subunit gp130, as removal of both gp130 and SOCS3 substantially decreased axon regeneration.

Several molecules signal through gp130 to promote axon growth, including interleukin-6, cardiotrophin-1 and ciliary neurotrophic factor (CNTF). The researchers found that only the expression of CNTF was increased after injury. What's more, if CNTF was administered in conjunction with deletion of SOCS3, axon regeneration was greatly enhanced.

These results support a model where the intrinsic regenerative capacity of neurons is constrained by SOCS activity. Targeting this limiting mechanism may provide a new therapeutic strategy to enhance repair after CNS injury. —*KDS*

■ MUSCLE DISEASE

Follow your nose

Odorant receptors don't just mediate the perception of smell—they are also involved in the chemotaxis of sperm and the proliferation of prostate cancer cells. Now, a study in mice suggests that muscle regeneration also relies on these receptors.

Christine Griffin *et al.* observed that the expression of multiple odorant receptors increases during myogenesis and regeneration. When they focused on the activity of one mouse odorant receptor called MOR23, they discovered that it helps regenerating muscle cells migrate and adhere to one another, and they also found that the cells release a ligand for MOR23 during regeneration.

When the team overexpressed MOR23 during regeneration, muscles branched less and enlarged—suggesting that the upregulation of odorant receptor expression could be a potential strategy for muscular dystrophy therapies. (*Dev. Cell* **17**, 649–661; 2009). —*MW*

■ AUTOIMMUNITY

Protecting the pancreas

Depleting B lymphocytes benefits people with type 1 diabetes (*N. Engl. J. Med.* **361**, 2143–2152).

Type 1 diabetes is associated with T lymphocyte–mediated autoimmune responses, but there is evidence that B lymphocytes may also be involved. Mark Pescovitz *et al.* carried out a phase 2 clinical study to test the effect of B lymphocyte depletion on type 1 diabetes using the monoclonal antibody rituximab.

A group of 78 patients received either placebo or four doses of rituximab. One year later, the level of C peptide—the peptide that results from the processing of proinsulin to insulin—was higher in them than in the placebo group after a meal, indicating the preservation of pancreatic islet function in the antibody-treated patients.

As rituximab is already used to treat certain forms of blood cancers, its use against type 1 diabetes is a tantalizing possibility. —*JCL*

■ FEVER PHYSIOLOGY

Bone and brain

A ligand-receptor pair best known for affecting bone remodeling is now implicated in fever and the regulation of body temperature (*Nature* **462**, 505–509).

In addition to their expression in the bone, receptor activator for nuclear factor-B and its ligand (RANK and RANKL) are expressed in the brain. To ask what these proteins might be doing there, Reiko Hanada *et al.* injected RANKL into the brains of mice and rats and found that it triggered fever. Further research shows that the proteins operate in astrocytes and are linked up to known thermoregulatory pathways.

In addition, the researchers implicated RANK and RANKL in the regulation of basal body temperature in females. They also identified two children with RANK mutations and an impaired fever response. The new findings provide a note of caution for efforts to target RANK and RANKL to treat bone disease such as osteoporosis. —*CS*

Written by Victoria Aranda, Kevin Da Silva, Anna Kushnir, Juan Carlos López, Charlotte Schubert & Melinda Wenner

New from NPG

Innate immune and chemically triggered oxidative stress modifies translational fidelity.
Netzer, N. *et al. Nature* **462**, 522–526; 2009.
Oxidative stress triggers a mechanism that results in the increased incorporation of damage-resistant methionine into proteins.

Rewiring of hindlimb corticospinal neurons after spinal cord injury
Ghosh, A. *et al. Nat. Neurosci.* published online, doi:10.1038/nn.2448 (13 December 2009).
After spinal cord injury causing paralysis of the hind limbs, the brain region sensing input from the unaffected limb rewires and expands into areas corresponding to the affected limb.

Regulation of adaptive behaviour during fasting by hypothalamic Foxa2.
Silva, J.P. *et al. Nature* **462**, 646–560; 2009.
Foxa2 can act as a metabolic sensor in the brain to integrate metabolic signals, adaptive behavior and physiological responses.

The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs.
Wellner, U. *et al. Nat. Cell Biol.* **11**, 1487–1495; 2009.
A protein previously implicated in metastasis may also affect cancer stem cells.

Cancer-associated IDH1 mutations produce 2-hydroxyglutarate.
Dang, L. *et al. Nature* **462**, 739–744; 2009.
A mutation common in human brain cancers results in the accumulation of a metabolite that contributes to formation and malignant progression of the tumor.

X-ray structure, symmetry and mechanism of an AMPA-subtype glutamate receptor.
Sobolevsky, A.I., Rosconi, M.P. & Gouaux, E. *Nature* **462**, 745–756; 2009.
Findings should aid in the development of drugs against a range of conditions affected by the glutamate receptor.