■ METABOLISM

Immunity and insulin

A molecule that may link nutrient sensing with pathogen sensing has been identified (*Cell* **140**, 338–348).

Double-stranded RNA–dependent protein kinase (PKR) is a key microbe detector. Upon detection of viral RNA, PKR activates the proinflammatory mediator JNK and inhibits the protein translation regulator eIF-2α—thereby coordinating an inflammatory response with inhibition of viral protein synthesis. But activating JNK is also known to inhibit insulin signaling.

Takahisa Nakamura *et al.* asked whether PKR also works with other factors that lead to insulin resistance, such as excess lipids and endoplasmic reticulum stress. Examining models of obesity in which these two factors occur, the researchers found activation of PKR in the liver and fat. Such PKR activation in turn led to inhibition of insulin signaling partly through direct inhibition of IRS1. Genetic knockout of PKR reduced diet-induced obesity and improved insulin sensitivity.

These findings suggest that PKR is a central node in the stress response and that it mediates the inflammation and insulin resistance that results from excess nutrients or pathogen infection. These results may also provide an explanation for the oft-seen association between viral infection and diabetes. —*RL*

■ INFLAMMATORY DISEASE

Platelet bombs

Fragments of platelets accumulate in the joints of people with rheumatoid arthritis, where they fuel painful inflammation, according to new work in human cells and in mice (*Science* **327**, 528–529, 2010).

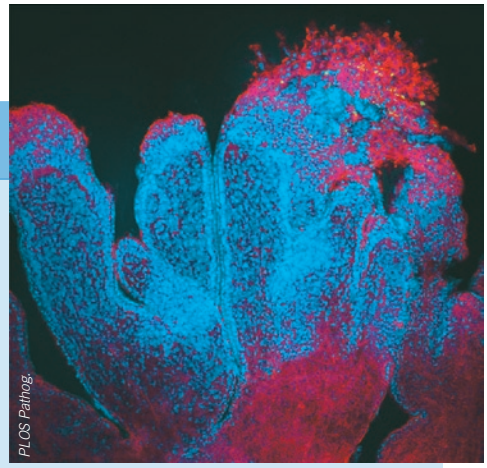
Platelets are untidy structures that can shed microparticles. Eric Boilard *et al.* observed that these particles accumulate in the joints of people affected with rheumatoid arthritis. They provide evidence that collagen, which is present in affected joints, promotes the shedding of microparticles via a receptor on platelets, collagen receptor glycoprotein VI. The microparticles in turn supply interleukin-1, a cytokine that promotes joint inflammation.

This cycle of inflammation presents potential opportunities for therapeutic intervention. The researchers found, for instance, that depleting platelets could alleviate symptoms in a mouse model of the disease. More targeted therapies could potentially focus on collagen receptor glycoprotein VI, particularly considering that mice or humans without this protein are healthy.

The findings dovetail with studies of platelets in atherosclerosis, where they have been shown to also have a proinflammatory role. —*CS*

REPRODUCTIVE BIOLOGY

The placenta pushes back



L. monocytogenes gains entry to the placenta through only a small population of cells (top right; bacteria are green, actin is red and DNA is blue).

Most of the time, exposure to *Listeria monocytogenes* during pregnancy is ultimately harmless, but the intracellular microbe can reach the placenta and fetus. There it can cause spontaneous abortion, stillbirth or preterm labor. Jennifer Robbins *et al.* examine how the bacterium ultimately gains entry and uncover some of the roadblocks in the way (*PloS Pathog.* 6, e100733).

In first-trimester human placental organ cultures, the researchers examined which cells were most susceptible to infection. They homed in on a small population of cells, dubbed extravillous cytotrophoblasts. These cells, which anchor the placenta to the uterine lining, are not in direct contact with maternal blood. Such cells, however, are in contact with maternal immune cells, which the researchers speculate may provide a source of the bacterium. The findings, say the researchers, might help explain why almost all placental pathogens have intracellular life cycles.

The researchers also examined a large population of cells, called syncytiotrophoblasts, that line the surface of the placenta and are bathed in maternal blood. In contrast to previous reports, these cells were highly resistant to infection. —*CS*

■ NEUROSCIENCE

Fast-acting antidepressants

Blocking adrenergic α_2 receptors may accelerate the action of antidepressants, according to studies in rats (*J. Neurosci.* **30**, 1096–1109).

Like antidepressants, compounds that target adrenergic α_2 receptors can also affect mood states. But it has been unclear whether such compounds have similar biological effects to antidepressants—such as the neurogenesis and increased expression of neurotrophic factor that occurs with prolonged use. Nor has the interaction between the two drug types been explored.

Sudhirkumar Yanpallewar *et al.* examined adult rat hippocampal progenitors *in vitro* and found that they expressed adrenergic α_2 receptors. Exposing these cells to α_2 agonists decreased their proliferation. By contrast, administration of an α_2 antagonist together with an antidepressant promoted progenitor proliferation, the maturation of newborn neurons and the increase in trophic factors characteristic of antidepressant use. *In vivo*, the same drug combination resulted in behavioral changes in the rats within one week, markedly faster than the three weeks necessary for antidepressants alone.

Future studies may investigate the mechanistic basis of the effect of adrenergic α_2 receptors. —*JCL*

Death protein in stroke

Neurons die during stroke in part through an excess influx of calcium through glutamate receptor channels. A report by Weihong Tu *et al.* now shows that the activity of death-associated protein kinase-1 (DAPK1) enhances this influx (*Cell* **140**, 222–234).

A previous report had shown that DAPK1 inhibitors could block neuron death due to stroke in rats. In the current work, the researchers found an increase in the binding of DAPK1 to the glutamate receptor protein complex in the cerebral cortex of mice subjected to stroke. Expressing DAPK1 and the glutamate receptor in cultured cells led to enhanced conductance through this receptor channel via phosphorylation of the glutamate receptor subunit NR2B.

Cultured cortical neurons lacking DAPK1 were less susceptible than neurons expressing the protein to death due to oxygen and glucose deprivation, conditions mimicking stroke. In mice lacking DAPK1, neuronal death after stroke and infarction size were reduced. Treatment of mice with a cell-permeable peptide that blocked the interaction between DAPK1 and the glutamate receptor reduced brain damage and improved neurological function after stroke. —*EC*

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■ CANCER

No exit for exosomes

In people with cancer, a particular subset of myeloid cells can promote tumor growth by fending off the immune system. Experiments in mice now uncover one way that tumors activate the immunosuppressive function of such cells, dubbed myeloid-derived suppressor cells (MDSCs).

Previous researchers had found that secreted microparticles, called exosomes, from tumor cells could activate MDSCs. Fanny Chalmin *et al.* examine the molecular steps behind this activation (*J. Clin. Invest.* **120**, 457–471, 2010). The researchers show that heat shock protein-72 (Hsp72) on the exosome surface interacts with its known receptor, Toll-like receptor 2, on MDSCs. This interaction, via interleukin-6, leads to the phosphorylation and activation of signal transducer and activator of transcription-3 (Stat3), which was required for the ability of MDSCs to inhibit T cell proliferation and promote tumor cell metastasis. Silencing Hsp72 in tumor cells, or chemically blocking the release of tumor exosomes, halted the whole cascade.

The researchers next examined 11 people with cancer, who were treated with amiloride. This diuretic is an analog of the compound the authors used experimentally, and it is thought to block exosome release. These individuals showed reduced Stat3 phosphorylation in MDSCs over 3 weeks of treatment and decreased MDSC function *ex vivo*. It remains to be seen whether amiloride treatment translates to enhanced antitumor immunity and improved patient outcome in a controlled setting. —*AF*

■ INFECTIOUS DISEASE

After the flu

Many people who die from influenza succumb not to the virus itself but to secondary infections from microbes such as *Streptococcus pneumoniae*. Using a mouse model, Amanda Jamieson *et al.* now examine the effect of such coinfection (*Cell Host Microbe*, **7**, 103–114).

The researchers infected mice first with influenza and then with *Listeria monocytogenes*. Although this bacterium is not often associated with influenza, the authors chose it because it models systemic bacterial infection. They found that infection with influenza strongly suppressed the systemic antibacterial response. This effect was mediated through an increase in the production of glucocorticoids through a cytokine-independent mechanism. Glucocorticoids are produced in response to stress and are known to suppress inflammation.

Compared to wild-type mice, mice lacking glucocorticoids were better able to suppress the secondary bacterial infection. But such mice ultimately died from the effects of an excessive inflammatory response.

The study highlights how glucocorticoids and the stress response may help set the balance between immune defense and immune pathology. —*CS*

■ REPRODUCTIVE BIOLOGY

p53 and premature labor

The risk of premature labor increases with the age of the mother, but the causes for this remain unknown. New insights arise from a study in mice showing how diminished uterine activity of the guardian protein p53 can induce preterm birth (*J. Clin. Invest.* doi:10.1172/JCI40051).

J. Clin. Invest.

Sites of implantation (blue) in the mouse uterus. Ovaries in blue at the top.

p53 is a ubiquitous regulator of gene expression and is essential in tissue development and stress response. But, owing to its widespread surveillance function, it is difficult to decipher p53's contribution to isolated physiological processes such as pregnancy.

Yasushi Hirota *et al.* overcame this limitation by selectively inactivating p53 in uterine cells and monitoring pregnancy in these genetically modified mice. The authors observed that, although the initial steps of embryonic development were unaffected by loss of p53, the growth of the supporting uterine stroma was compromised.

Decreased p53 signaling led to impaired formation of the maternal placenta lining and resulted in preterm labor and neonatal death.

As previous studies have shown that p53 abundance physiologically decreases in aging mice, the present findings could be relevant to age-related pregnancy defects. —*VA*

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New from NPG

Systemic signals regulate ageing and rejuvenation of blood stem cell niches.
Mayack, S.R., Shadrach, J.L., Kim, F.S. & Wagers, A.J. *Nature* **463**, 495ñ500.
The changes with age in stem cell support niches are reversible by exposure to young circulation or to the longevity regulator insulin-like growth factor-1.

miR-9, a MYC/MYCN-activated microRNA, regulates E-cadherin and cancer metastasis.
Ma, L. *et al. Nat. Cell Biol.* published online, doi:10.1038/ncb2024 (21 February).
The microRNA miR-9, a target of the Myc oncogene, controls tumor angiogenesis and the spread of breast cancer cells by regulating E-cadherin.

A combined method for producing homogeneous glycoproteins with eukaryotic N-glycosylation.
Schwarz, F. *et al. Nat. Chem. Biol.* published online, doi:10.1038/nchembio.314 (28 February).
Producing correctly glycosylated mammalian proteins in bacteria has been challenging, but this method provides a potentially general platform for producing eukaryotic N-glycoproteins in prokaryotes.

Axonal prion protein is required for peripheral myelin maintenance.
Bremer, J. *et al. Nat. Neurosci.* published online, doi:10.1038/nn.2483 (24 January).
Deletion of the cellular prion protin PrPC specifically in neurons results in a demyelinating disease in mice, pointing to a role for the noninfectious form of this hard-to-pin-down protein.

Regulation of hematopoietic stem cell differentiation by a single ubiquitin ligase-substrate complex.
Reavie, L. *et al. Nat. Immunol.* **11**, 207–215.
Post-translational modifications affect the stability of the transcription factor c-Myc and, in turn, control the differentiation of hematopoietic stem cells.

Hsp70 stabilizes lysosomes and reverts Niemann-Pick disease–associated lysosomal pathology.
Kirkegaard, T. *et al. Nature* **463**, 549–553.
Study of human cells opens door to new approaches to treat lysosomal storage disorders and cancer.