■ CANCER

Exosomes from the stroma

A recent paper adds a new facet to the role of the microenvironment in tumorigenesis, showing that stromal-derived exosomes can promote breast cancer cell migration and invasiveness by modulating signaling through the Wnt–planar cell polarity (PCP) pathway (*Cell* **151**, 1542–1556).

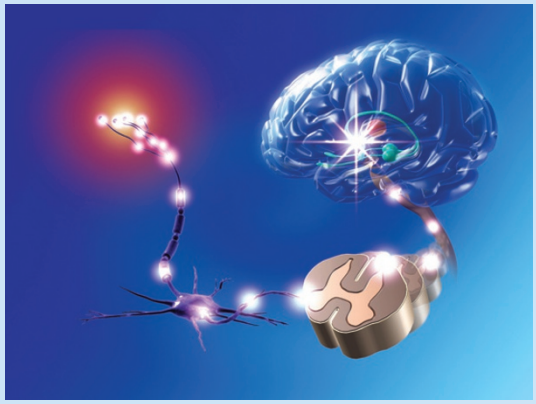
Valbona Luga *et al.* found that fibroblast-conditioned medium promoted the formation of protusions from breast cancer cells as well as their motility, and co-injection of fibroblasts and breast cancer cells into mice led to increased metastasis compared to the injection of cancer cells alone. They then showed that knockdown of core PCP pathway components in cancer cells abrogated the effects of fibroblasts on breast cancer cell motility, suggesting that the fibroblasts mediate motility through the PCP pathway. Similarly, the fibroblast-mediated effects required expression of the Wnt ligand Wnt11 in breast cancer cells. Treatment of the cancer cells with conditioned medium led to the asymmetric distribution of core PCP components and Wnt11 in cell protrusions, analogous to the distribution of such components in planar-polarized epithelial cells.

The authors then identified the active component of the conditioned medium as exosomes expressing the tetraspanin protein CD81. In a gene expression data set from human breast cancers, they showed that CD81 was significantly upregulated in the stroma associated with breast cancer compared with control breast tissue, suggesting that CD81 may also have a role in the tumor-associated stroma in human breast cancer.

Finally, Luga *et al.* provided mechanistic insights into how stromal exosomes mediate autocrine PCP signaling in breast cancer cells: the exosomes are taken up by the cancer cells by endocytosis, and Wnt11 then associates with the exosomes and is redistributed in the cancer cell, which the authors suggest is important for activating PCP signaling.—*MS*

PAIN

Painful communication



Marc Phares / Science Source

High levels of neuronal activity in pain-sensing neurons can cause structural and functional changes in those neurons that lead to chronic pain. Now, Manuela Simonetti *et al.* report that calcium entry into the nucleus of neurons in the spinal cord leads to changes in gene expression that are responsible for inducing pain (*Neuron* 77, 43–57).

The research team used calcium sensors to show that intense stimulation of spinal cord neurons, which can lead to chronic hyperalgesia (hypersensitivity to touch or temperature stimuli), causes an influx in calcium into the nucleus of those neurons. When they blocked nuclear calcium signaling in spinal cord neurons of mice by nuclear overexpression of calmodulin-binding protein 4, a protein that buffers signaling downstream of calcium-dependent calmodulin, this reduced hyperalgesia after inflammation, probably owing to an inability to activate the transcription factor CREB.

Using gene profiling, the authors found that pain-dependent nuclear calcium signaling reduced expression of the complement pathway component C1q. When the researchers reduced expression of C1q in the spinal cord, they showed that this increased pain, whereas administering C1q protein induced pain. C1q seemed to act by reducing the density of dendritic spines on neurons, although how exactly these molecules affect this process remains to be determined. —*EC*

■ METABOLISM

IL-13 controls blood sugar

Interleukin-13 (IL-13) is now shown to control hepatic glucose production, raising the possibility that targeting this cytokine may have therapeutic benefit against type 2 diabetes (*J. Clin. Invest.* **123**, 261–271).

Using mice lacking IL-13, Kristopher Stanya *et al.* found that the mice developed hyperglycemia and hepatic insulin resistance. Mechanistically, the authors showed that gluconeogenesis enzymes were upregulated in the livers of the knockout mice. They found evidence that, acting through Stat3, IL-13 directly inhibited the transcription of gluconeogenic genes in hepatocytes. Moreover, IL-13 lost the ability to suppress glucose production in hepatocytes lacking *Stat3* or an IL-13 receptor subunit.

As the immune system can directly regulate metabolic functions, it will be of interest to study the role of IL-13 in mice lacking this cytokine in specific cell populations to tease apart its direct effect on the liver from any additional effects on glycemic control via macrophages or other immune cells.—*JCL*

■ STEM CELLS

Promoting pluripotency

Poly(ADP-ribose) polymerase 1 (Parp1), a DNA-binding protein, can be used in place of c-Myc when reprogramming somatic cells to induced pluripotent stem cells (iPSCs).

Recent studies (Doege *et al. Nature* **488**, 652–655; Lai *et al. Proc. Natl. Acad. Sci. USA* **109**, 3772–3777) have shown that Parp1 activity is increased during nuclear reprogramming induced by the transcription factors Oct4, Sox2, Klf4 and c-Myc and is important for early epigenetic changes that enable reprogramming.

Guang-Yuh Chiou and colleagues (*J. Exp. Med.* **210**, 85–98) now report that Parp1 is induced downstream of c-Myc and increases the efficiency of iPSC reprogramming. c-Myc binds directly to the *Parp1* promoter and promotes Parp1 expression during reprogramming. As Parp1 is downstream of c-Myc, the investigators silenced Parp1 and found that it is required for reprogramming. Indeed, Parp1 can substitute for c-Myc during reprogramming, as iPSC reprogramming efficiency was similar in cells transfected with Oct4, Sox2 and Parp1 compared with those transfected with Oct4, Sox2 and c-Myc. These iPSCs can then be injected into blastocysts to generate competent adult chimeric mice.—*KDS*

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