Cancer: lost direction

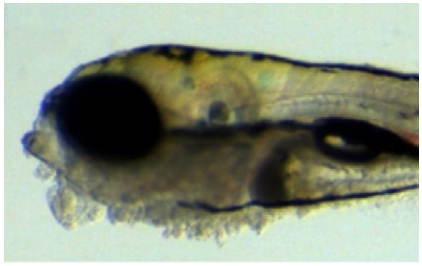

Image reproduced from *PLoS Genet*. (Reischauer et al., 2009).

Normal epithelial cells create contiguous cell sheets that cover the surfaces of organs or the body surface, and that exhibit a distinctive apical and basal surface. Loss of this polarity contributes to epithelial-to-mesenchymal transition (EMT) and is associated with invasive phenotypes of cancer. Mutations to genes that regulate the polarized distribution of cellular proteins are known to contribute to cancer progression, but how polarity and tumorigenesis are linked is not known. Reischauer et al. found that a gene that regulates the polarity of epithelial cells in zebrafish, *lethal giant larvae 2* (*lgl2*), suppresses EMT and malignant growth. ErbB2 signaling, which is disrupted in some forms of human cancer, is necessary for the genesis of neoplasia in zebrafish that lack the *lgl2* gene. Thus, lgl2 is a tumor suppressor gene in vertebrates and Lgl2 mutant zebrafish should provide a valuable new cancer model.

Reischauer, S., Levesque, M. P., Nüsslein-Volhard, C. and Sonawane, M. (2009). Lgl2 executes its function as a tumor suppressor by regulating ErbB signaling in the zebrafish epidermis. *PLoS Genet*. **5**, e1000720.

Neurology: no pain, no VGLUT3

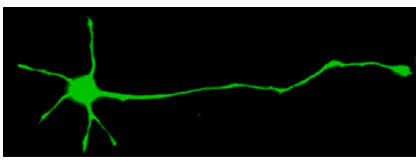

Image reproduced from Cosker et al. (2008). *J. Cell Sci.* **121**, 796-803.

Chronic pain stemming from hypersensitivity to slight touch is often caused by injury or inflammation. This is a common and debilitating medical condition. Since the type of sensory neurons responsible for this persistent pain after injury and the molecular pathways involved are both unknown, patient treatment is limited to mitigating pain. However, Seal et al. have identified a specific subset of sensory neurons that express a rare transporter molecule called VGLUT3. This transporter enables neurons to release an excitatory neurotransmitter, glutamate. Researchers engineered mice that lack VGLUT3 and discovered that these mice no longer display injury-induced pain hypersensitivity. Conversely, researchers produced a different strain of mice that express VGLUT3 normally, but only in neurons that also emit a traceable green light. The VGLUT3-expressing neurons responded normally to light touch however, after injury, these neurons produced pain signals under similar conditions. This discovery suggests that drugs targeting the VGLUT3 pathway may inhibit the transmission of pain associated with hypersensitivity following injury.

Written by M.R.

Seal, R. P., Wang, X., Guan, Y., Raja, S. N., Woodbury, C. J., Basbaum, A. I. and Edwards, R. H. (2009). Injury-induced mechanical hypersensitivity requires C-low threshold mechanoreceptors. *Nature* Nov 15 [Epub ahead of print] [doi:10.1038/nature08505].

Inflammation: migratory cells spread arthritis

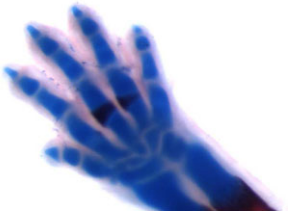

Image reproduced from Matsumoto et al. (2009). *Development* **136**, 2825-2835.

In rheumatoid arthritis (RA), inflammation of the tissues in and around the joints often causes pain, stiffening and joint deformity. Initially, RA is often confined to a single or limited number of joints, but eventually spreads by mechanisms that are not understood. Lefèvre et al. show that migratory fibroblasts known as rheumatoid arthritis synovial fibroblasts (RASFs), which mediate inflammation in human joint tissue, migrate to other joints after transplantation into immunodeficient mice. The RASF cells also move into the adjacently transplanted cartilage. Medical treatment for RA is confined to lifelong physical therapy, corrective surgery and lifelong treatment with anti-inflammatory drugs, many of which have toxic side effects. The contribution of cell migration to the spread of the disease in this mouse model may provide some insight into how RA progression might be inhibited.

Lefèvre, S., Knedla, A., Tennie, C., Kampmann, A., Wunrau, C., Dinser, R., Korb, A., Schnäker, E. M., Tarner, I. H., Robbins, P. D. et al. (2009). Synovial fibroblasts spread rheumatoid arthritis to unaffected joints. *Nat. Med.* Nov 8 [Epub ahead of print] [doi:10.1038/nm.2050].

Infectious disease: CO_2 levels contribute to infection

In some diseases that affect pulmonary function, such as cystic fibrosis and chronic obstructive pulmonary disease (COPD), carbon dioxide levels in the blood accumulate owing to the inability of the body to properly regulate ventilation. The resulting condition is called hypercapnia acidosis, which can disrupt cardiac and neurological function, and impair the immune response. Helenius et al. found that when Drosophila were exposed to high levels of carbon dioxide, they changed their gene profiles and suppressed their production of antimicrobial peptides. Hypercapnia in flies impaired their ability to survive infection with a variety of bacterial strains by inhibiting their resistance to infection. In mammals, hypercapnia can suppress immune function through its inhibition of the NFκB pathway. In hypercapnic flies, the downregulated immune peptides are regulated by Relish, which is a conserved member of this pathway. Flies exposed to high carbon dioxide levels also exhibit developmental and reproductive changes. The genetic tractability of Drosophila, and the molecular conservation of its innate immune response with mammals, make this a useful model to understand some of the ways that hypercapnia acidosis impairs immunity and possibly contributes to the poor outcomes of patients with obstructive lung disease.

Helenius, I. T., Krupinski, T., Turnbull, D. W., Gruenbaum, Y., Silverman, N., Johnson, E. A., Sporn, P. H., Sznajder, J. I. and Beitel, G. J. (2009). Elevated CO_2 suppresses specific Drosophila innate immune responses and resistance to bacterial infection. *Proc. Natl. Acad. Sci. USA* **106**, 18710-18715.