■ SCHIZOPHRENIA

Going retro

Retrotransposons are movable genetic elements that are found throughout the genome. Insertion of new retrotransposon copies in or near genes could be involved in disease pathogenesis. Now, Miki Bundo and colleagues have identified a high copy number of the retrotransposon L1 specifically in neurons within the postmortem prefrontal cortex from individuals with schizophrenia compared to normal controls and other psychiatric diseases (*Neuron* doi:10.1016/j.neuron.2013.10.053, 2 January 2014). Using whole-genome sequencing of brain DNA from the patients with schizophrenia versus control subjects, the authors found that L1 insertions sites in individuals with schizophrenia often occur in or near genes linked to neuronal and synaptic function.

Mechanistically, maternal immune activation in pregnant mice with the immunostimulant poly-I:C led to increased L1 copy number in the offspring. The findings suggest how early environmental risk factors, which have been previously linked to increased disease risk, could drive genetic changes that contribute to the pathogenesis of schizophrenia or other illnesses.—*EC*

INFLAMMATION

Post-worm lung repair

Science Source

A new study shows how the cytokine interleukin-9 (IL-9) indirectly promotes tissue repair after worm-induced inflammatory damage in the lung by inducing the survival and activation of type 2 innate lymphoid cells (ILC2s) (*J. Exp. Med.* 210, 2951–2965, 2013).

Previous studies showed that ILC2s produce IL-9 during lung inflammation and contribute to host immunity in helminth infection in the gut. Jan-Eric Turner and his colleagues found that ILC2s in lungs are also the main producers of IL-9 in response to tissue damage caused during the lung stage of a worm infection. Using mice lacking the IL-9 receptor, the authors also showed that accumulation of ILC2s—but not T helper type 2 cells—during worm-induced lung injury requires IL-9, which induces the antiapoptotic protein BCL3. In ILC2s, this IL-9–mediated autocrine survival signal resulted in increased secretion of type 2 cytokines and amphiregulin and recruitment and activation of myeloid cells, which in concert promote lung damage repair at chronic stages.

Future studies should clarify how this IL-9 feedback loop may be halted after repair to clear ILC2s from the lungs to prevent potential harmful effects of these cells in the lung.—*CP*

■ HIV INFECTIONS

T cell loss in HIV infection

Killing of bystander or resting CD4$^+$ T cells accounts for the majority of T cell loss in lymphoid organs in individuals infected with HIV and contributes to the development of AIDS. This T cell depletion was recently attributed to abortive viral infection in which HIV RNA is reverse transcribed but does not integrate into the host cell DNA. Warner Greene and his colleagues now report in two papers that such abortive infection activates sensing of the viral DNA by interferon-gamma–inducible protein 16 (IFI16) and leads to inflammatory cell death—pyroptosis—in the uninfected cells.

Doitsh *et al.* (doi:10.1038/nature12940, 9 December 2013) showed that death of resting CD4$^+$ T cells owing to nonproductive HIV-1 infection did not involve apoptosis but rather pyroptosis, which is caspase-1 dependent and leads to release of the proinflammatory cytokine interleukin-1β. Inhibiting expression or activity of caspase-1 blocked T cell death *in vitro*.

To identify the cellular sensor of abortive infection, Monroe *et al.* (doi:10.1126/science.1243640, 19 December 2013) used HIV-1 DNA as bait and showed they could affinity-purify IFI16 from primary human tonsillar CD4$^+$ T cell lysates. IFI16 bound both HIV double-stranded DNA and more weakly to single-stranded DNA. Silencing of IFI16 in CD4$^+$ T cells in culture reduced caspase-1 activation and prevented cell death induced by abortive HIV infection.

The researchers propose that sensing of abortive infection of resting CD4$^+$ T cells by IFI16 and consequent pyroptosis may recruit new T cell targets for infection, promoting a cycle of T cell depletion and inflammation. Blocking this cycle might prevent the loss of CD4$^+$ T cells and progression to AIDS.—*AF*

■ METABOLIC DISEASES

Dietary fiber takes a circuitous route

The beneficial metabolic effects of soluble dietary fiber are thought to be owing to its fermentation by gut bacteria into short-chain fatty acids. Gilles Mithieux and his colleagues found that the healthful effects of these fatty acids depend on their stimulation of intestinal gluconeogenesis, in part through a gut-brain neural circuit (*Cell*, **156**, 84–96, 2014).

Mice fed soluble fiber or either of two short-chain fatty acids—butyrate or proprionate—showed an improved metabolic profile, with increased glucose tolerance and insulin sensitivity. Both butyrate and proprionate stimulated intestinal gluconeogenesis, but they use different mechanisms. Whereas butyrate had direct effects on intestinal cells, propionate acted indirectly, via the nervous system. In this neural circuit, proprionate seems to act through the fatty acid receptor FFAR3 on nerve fibers of the portal vein, resulting in activation of several regions in the brain and spinal cord.

Intestinal gluconeogenesis was needed for the beneficial effects of soluble fiber or short fatty acids, as neither dietary intervention improved the metabolic profile of mice with an intestine-specific deficiency of the key gluconeogenic enzyme glucose-6-phosphatase.—*MB*

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