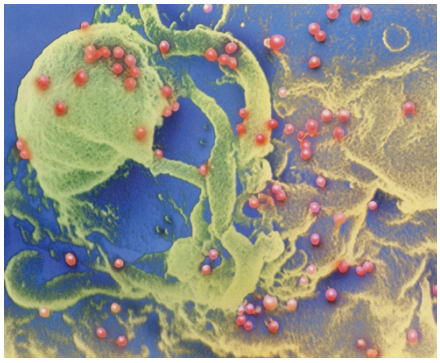
■ HIV INFECTIONS

Editing the way to therapy for HIV

The development of genome-editing tools, such as zinc finger nucleases, could have promising therapeutic possibilities. One group has now shown that infusion of autologous CD4$^+$ T cells after modification of the *CCR5* gene—the major co-receptor for HIV—in patients is safe (*N. Engl. J. Med.* **370**, 901–910, 2014).



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Tebas *et al*. enrolled 12 patients with HIV infections that were undetectable in the blood during highly active antiretroviral treatment in a trial in which the patients received one dose of CD4-enriched T cells, consisting of 11–28% T cells with CCR5 disrupted by zinc finger nuclease modification. The infusion increased the overall number of circulating CD4$^+$ T cells. These cells, however, declined in number upon withdrawal of antiretroviral therapy, though the decline was smaller in the CCR5-engineered cells, and the overall CD4$^+$ T cell number was still higher than before infusion. There was also a decrease in viral RNA in four patients who were able to finish the 12-week withdrawal, and only one individual had an adverse effect due to the infusion.

Although the number of patients enrolled in the study is too small to make any strong conclusions regarding safety and efficacy, it seems that gene editing to create immune cells resistant to HIV infection might be safe and shows promise for the treatment of HIV. —*HS*

■ MEDICAL GENETICS

Narrowing down obesity genes

Genome-wide association studies (GWAS) have previously shown that variants in introns of the *FTO* gene are associated with a predisposition to obesity and type 2 diabetes in humans. Now a study (*Nature* doi:10.1038/nature13138, 12 March 2014) in human tissue and mouse models show that these variants alter the gene expression of transcription factor *IRX3*, and not *FTO*, which was formerly thought to be the key player in obesity in this region.

Previous studies have failed to link *FTO* gene variants with alterations in its expression in humans, which prompted Smemo *et al*. to use techniques that allow the identification of long-range chromatin interactions of the variants. In the brains of embryonic and adult mice, these obesity-associated variants physically interacted with the *Irx3* promoter. Furthermore, in tissues from human brains, *IRX3* expression correlated with the presence of single nucleotide polymorphisms associated with increased body-mass index. The authors found that mice lacking *Irx3* were resistant to high-fat diet–induced obesity and insulin resistance and had 'browning' of white adipose tissue, suggesting that *Irx3* may regulate energy homeostasis.

The authors' tale is a cautionary one, as it underscores the need to rethink how we follow up GWAS hits in noncoding intervals to confirm candidate target genes in human diseases. —*HS*

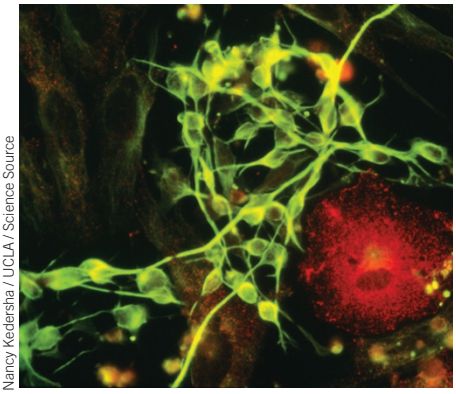
■ AMYOTROPHIC LATERAL SCLEROSIS

Mayhem-making microglia

Glial cells contribute to motor neuron death in amyotrophic lateral sclerosis (ALS), but the mechanisms by which they do so have been unclear. Now, Ashley Frakes and her colleagues identify inflammatory nuclear factor-κB (NF-κB) signaling in microglia as a driver for motor neuron death and disease progression in mouse models of ALS (*Neuron* **81**, 1009–1023, 2014).

NF-κB activation is known to occur in glia in individuals with ALS, and the researchers found that this was also the case within the microglia of mice with mutations in superoxide dismutase (SOD) that cause ALS in humans. Inhibiting NF-κB by genetic ablation of its activator in astroglia did not reduce neuron death in the mice, but inhibiting NF-κB in microglia did protect neurons and extended the lifespan of the mice. Activating NF-κB in microglia in wild-type mice led to motor neuron death, probably owing to conversion of the microglia to a proinflammatory phenotype.

The findings suggest that targeting NF-κB signaling in microglia could be a potential therapeutic approach to slow ALS pathogenesis. —*EC*



Nancy Kedersha / UCLA / Science Source

■ NUTRITION

Dietary protein and lifespan

Two reports in *Cell Metabolism* suggest that the protein composition of the diet has a strong effect on healthspan.

Samantha M. Solon-Biet and her colleagues (*Cell Metab.* **19**, 418–430, 2014) explored the effects of 25 different *ad libitum* diets on the lifespan and cardiometabolic phenotypes of mice. The 25 diets varied by protein, carbohydrate and fat content, as well as by energy density. Mice fed diets relatively low in protein and high in carbohydrates lived longer and had better metabolic health than those on a higher protein, lower carb diet.

The study by Levine *et al*. (*Cell Metab.* **19**, 407–417, 2014) examined data from 6,831 individuals from the US National Health and Nutrition Examination Survey (NHANES) III study. A self-reported low-protein diet was found to be associated with lower overall, cancer-related and diabetes-related mortalities. This was only true for people between the ages of 50 and 65 when the study was started. For those aged 65 or older when first surveyed, a high-protein diet (especially from plants) was found to be more protective for such mortalities. The authors' data suggests that lower insulin-like growth factor-1 signaling explains these beneficial effects in the younger cohort. They also hypothesize that older people have a harder time absorbing protein, leading to frailty, so a low-protein diet exacerbates this condition. —*RL*

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