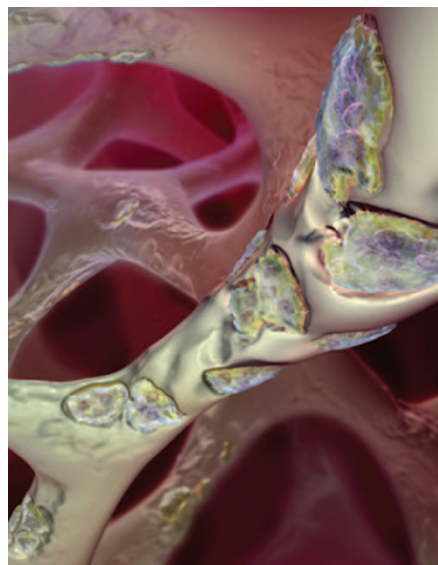


be needed to show whether this new BAT regulating mechanism is also active in humans and whether it could be explored as a relevant therapeutic target for metabolic and obesity disorders. —VA

## ■ BONE

### Autoantibodies target bone

Autoantibodies against proteins marked with a type of post-translational modification called citrullination are found in people with rheumatoid arthritis and are one of the strongest risk factors for bone destruction in this disease. A recent study now directly links the formation of these antibodies to bone loss in rheumatoid arthritis, indicating that the autoantibodies act on osteoclasts, the bone cells responsible for bone resorption (*J. Clin. Invest.* **122**, 1791–1802).



Gary Carlsson / Photo Researchers, Inc.

Ulrike Harre *et al.* found that the presence of anti-citrullinated protein antibodies (ACPAs) is associated with increased amounts of serum markers of bone resorption in people with rheumatoid arthritis. They affinity-purified autoantibodies against mutated citrullinated vimentin from patients; the production of these antibodies is highly specific to people with rheumatoid arthritis. *In vitro*, these purified ACPAs bound to the surface of osteoclast progenitors and induced their differentiation into mature osteoclasts and also increased osteoclast-mediated bone resorption.

The authors then injected the purified ACPAs into immunodeficient *Rag1<sup>-/-</sup>* mice, leading to systemic bone loss. This bone loss seemed to be mediated through an increase in

osteoclast precursor numbers and increased osteoclast differentiation in response to ACPAs. These effects may depend on tumor necrosis factor- $\alpha$ , as the authors observed increased amounts of this inflammatory cytokine, which is known to induce osteoclastogenesis, in the mice treated with ACPAs.

This work thus provides new insights into the interactions between the immune system, inflammation and bone in rheumatoid arthritis. —MS

## ■ GENETICS

### Somatic mutations in brain

A new study highlights an intriguing role for somatic mutations restricted to the brain in a developmental brain disorder, hemimegalencephaly (HMG) (*Neuron* **74**, 41–48).

HMG is an epileptic brain disorder characterized by the enlargement and malformation of one hemisphere of the brain. Given this regional selectivity of the deformation, it has been suggested that HMG may be caused by a somatic mutation limited to the brain, and Annapurna Poduri *et al.* now provide evidence to support this hypothesis.

The authors analyzed resected brain tissue samples from eight individuals with HMG and found that two of the samples showed trisomy of chromosome 1q, but, in one of the individuals, the blood sample did not show this genetic aberration. Of the genes on chromosome 1q, Poduri *et al.* suggest *AKT3* as a strong candidate gene for HMG, because *AKT3* deletions have been previously associated with microcephaly in humans and mice. Moreover, somatic activating mutations in the related genes *AKT1* and *AKT2* have been associated with human overgrowth syndromes. The authors also found a somatic activating mutation of *AKT3* (E17K) in the brain of one individual with HMG.

These results suggest that somatic mutations in the brain could have an important role in neurogenetic disease, although the mechanisms by which they occur remain to be determined. They also bring up an interesting parallel between somatic mutations in cancer and in brain disease: somatic *AKT3* mutations have also been identified in cancer, but none of the individuals studied by Poduri *et al.* had any form of cancer, suggesting that *AKT3* mutations may result in different outcomes in different cellular contexts. —MS

Written by Victoria Aranda, Eva Chmielnicki, Alison Farrell, Carolina Pola and Meera Swami

## New from NPG

### Apolipoprotein E controls cerebrovascular integrity via cyclophilin A

Bell, R.D. *et al.* *Nature* doi:10.1038/nature11087 (16 May).

The authors provide a mechanistic link between the *APOE4* gene and blood-brain-barrier defects by showing that *APOE4* expression in mice activates a pathway in pericytes involving cyclophilin A (CypA) activation. This leads to neuronal uptake of blood-derived neurotoxic proteins. Thus, CypA may be a potential target for treating *APOE4*-mediated neurovascular injury, such as in Alzheimer's disease.

### PPAR- $\gamma$ is a major driver of the accumulation and phenotype of adipose tissue T<sub>reg</sub> cells

Cipolletta, D. *et al.* *Nature* doi:10.1038/nature11132 (16 May).

This study uncovers a new aspect to the action of the thiazolidinedione drug pioglitazone, used in the treatment of type 2 diabetes. The authors show that a population of regulatory T cells in the visceral fat are controlled by peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ) and that the expression of PPAR- $\gamma$  in these cells is important for the insulin-sensitizing activity of pioglitazone.

### Detectable clonal mosaicism and its relationship to aging and cancer

Jacobs, K.B. *et al.* *Nat. Genet.* doi:10.1038/ng.2270 (6 May).

### Detectable clonal mosaicism from birth to old age and its relationship to cancer

Laurie, C.C. *et al.* *Nat. Genet.* doi:10.1038/ng.2271 (6 May).

Two new studies find mosaicism for large chromosomal abnormalities in peripheral blood samples from individuals in the general population. The frequency of these genetic changes increases with age and is associated with an increased risk of subsequently developing a hematological cancer.

### Adolescent impulsivity phenotypes characterized by distinct brain networks

Whelan, R. *et al.* *Nat. Neurosci.* doi:10.1038/nn.3092 (29 April).

The authors examine the activation of brain networks in adolescents with attention-deficit hyperactivity disorder (ADHD) and those who had used drugs or alcohol using functional magnetic resonance imaging. They find that although both ADHD and substance abuse are associated with increased impulsiveness, different brain networks were activated in response to a task testing impulsiveness in these two contexts.