commonly found in lupus, but the source of these autoantigens remains unclear. Previous studies *in vitro* have suggested that neutrophils may be a potential source, as activation of neutrophils induces the release of complexes of nuclear antigens and antimicrobial peptides (termed neutrophil extracellular traps (NETs)). These complexes then trigger activation of plasmacytoid dendritic cells via Toll-like receptors and release of interferon-α from these cells.

To examine this proposed mechanism *in vivo*, Campbell *et al.* crossed lupus-prone mice with mice deficient in Nox2, which is required for NET release. Although neutrophils from these mice fail to produce NETs in response to phorbol myristate acetate (PMA), renal disease was worse than in lupus-prone mice with intact Nox2, suggesting NETs do not promote disease pathogenesis in this model. Loss of Nox2 increased the number of antibody-forming cells and also modified the autoantibody response. These findings suggest that future studies are needed to resolve how neutrophils contribute to the pathogenesis of lupus *in vivo* and to investigate the protective role of Nox2 in lupus. —*KDS*

■ KIDNEY

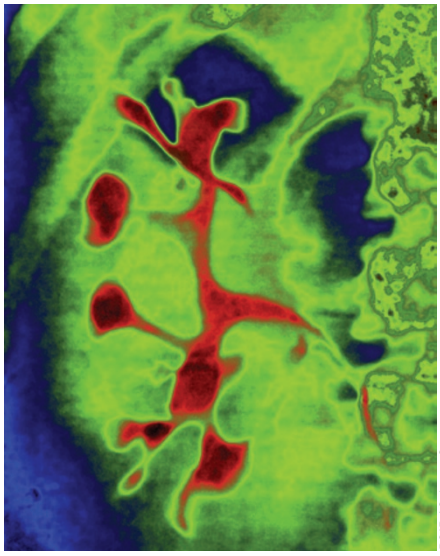
Going with the flow

A phase 3 clinical trial published in the *New England Journal of Medicine* (doi:10.1056/NEJMoa1205511) shows mixed results in the treatment of autosomal dominant polycystic kidney disease (ADPKD).

ADPKD is marked by renal fluid-filled cysts that eventually lead to kidney failure. Preclinical studies have suggested that the antidiuretic hormone vasopressin contributes to pathogenesis, and a previous 3-year open-label clinical trial showed that tolvaptan, a vasopressin receptor antagonist, reduces the rate of increase in kidney volume and the decline in glomerular filtration rate in 63 patients with ADPKD.

In the new study, Vincente E. Torres *et al.* report in a 3-year multicenter double-blind, placebo-controlled phase 3 clinical trial that tolvaptan had similar beneficial effects on 740 patients. But they also found that the tolvaptan-treated patients had more adverse events, such as increased thirst, increased urine production and hepatic injury. Overall approximately threefold more patients in the treated group discontinued the trial versus those in the placebo group.

Tolvaptan could eventually be approved to treat ADPKD, but clearly other treatment modalities are needed. Fortunately, basic research in this area has been proceeding well, and other targets are in the works.—*RL*



BSIP / Science Source

■ METABOLISM

Fine-tuning iron

Cells respond to iron deficiency through a well-characterized homeostatic response involving the RNA-binding proteins IRP1 and IRP2. Marina Bayeva *et al.* now reveal additional complexity to this response, identifying a new regulator, the protein tristetraprolin (TTP, *Cell Metab.* **16**, 645–657).

TTP is a mammalian homolog of RNA-binding proteins in baker's yeast that regulate iron homeostasis by destabilizing the mRNAs of iron-requiring proteins. The authors showed that TTP deficiency in mammalian cells made them more vulnerable to iron deprivation. Iron deprivation or inhibition of the kinase mTOR led to increased TTP expression, which in turn reduced the expression of specific mRNAs containing its target sequence. Unexpectedly, TTP bound and destabilized the mRNA of transferrin receptor 1 (TfR1), thereby inhibiting cellular iron uptake. TTP thus seems to act in opposition to the IRP1–IRP2 pathway, which stabilizes TfR1 mRNA, and the authors propose that in this way TTP may block excessive iron import. They then extended their cellular data to mice, showing that the hearts of mice lacking TTP had increased TfR1 expression.

It remains to be seen how this newly identified mTOR–TTP pathway might affect the dysregulation of iron homeostasis that occurs in individuals treated with mTOR inhibitors, such as rapamycin, or in a wide variety of disease states.—*MB*

Written by Michael Basson, Kevin Da Silva, Alison Farrell, Randy Levinson, Juan Carlos López, Carolina Pola and Meera Swami

New from NPG

Towards germline gene therapy of inherited mitochondrial diseases
Tachibana, M. *et al. Nature* doi:10.1038/nature11647 (24 October).
The authors assessed the feasibility of mitochondrial DNA replacement in human oocytes by spindle transfer, finding that the treated oocytes had a similar fertilization rate to control oocytes. Although over half the spindle transfer zygotes showed abnormal fertilization, the normally fertilized spindle transfer zygotes could develop to blastocysts and produce embryonic stem cells.

MyomiR-133 regulates brown fat differentiation through Prdm16
Trajkovski, M. *et al. Nat. Cell. Biol.* doi:10.1038/ncb2612 (11 November).
This study identifies miRNA-133 as a negative regulator of PRDM16, which is important for the differentiation of brown adipocytes. The authors showed that after mice were subjected to cold exposure, miRNA-133 is downregulated in brown fat and subcutaneous white adipose due to decreased expression of its transcriptional regulator Mef2.

The genetic landscape of mutations in Burkitt lymphoma
Love, C. *et al. Nat. Genet.* doi:10.1038/ng.2468 (11 November).

Recurrent mutation of the *ID3* gene in Burkitt lymphoma identified by integrated genome, exome and transcriptome sequencing
Richter, J. *et al. Nat. Genet.* doi:10.1038/ng.2469 (11 November).
Two groups identify a number of genes recurrently mutated in Burkitt lymphoma using comprehensive sequencing approaches. Both studies highlighted *ID3* as a frequently mutated gene in the lymphomas they analyzed. Mutations in *ID3* were shown to promote cell cycle progression and proliferation, and it may be a putative tumor suppressor gene.

The CD46-Jagged1 interaction is critical for human T_H1 immunity
Le Friec, G. *et al. Nat. Immunol.* doi:10.1038/ni.2454 (21 October).
The authors identify the Notch family member Jagged1 as a ligand for the complement regulator CD46. They show that disruption of the CD46–Jagged1 interaction reduces induction of T helper type 1 (T_H1) cells. Moreover, patients with Alagille syndrome, who have mutations in the gene encoding Jagged1, and people with CD46 mutations both show an impaired T_H1 response.