■ NEURODEVELOPMENTAL DISORDERS

Microcephaly mutations

A recent study provides new insights into the genetic underpinnings of a form of congenital microcephaly (*Neuron* **80**, 429–441).

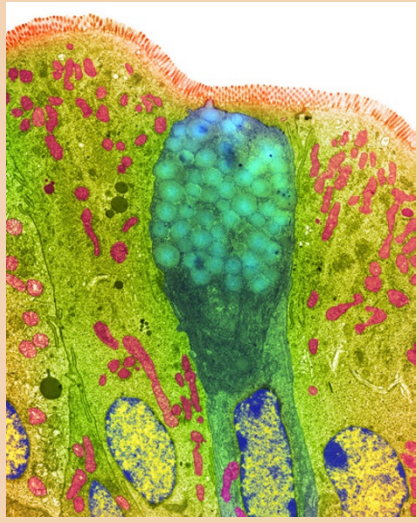
David Goldstein and his colleagues studied four families with a similar neurological syndrome consisting of microcephaly, intellectual disability and seizures. Using exome sequencing, the authors showed that the condition is caused by recessive mutations in the *ASNS* gene and identified three mutations (A6E, F362V and R550C) that lead to amino acid changes in the enzyme encoded by the gene, asparagine synthetase.

In vitro, the authors found that the A6E and F362V mutations led to reduced expression of asparagine synthetase, and the R550C mutation resulted in increased expression compared to the wild-type protein. Although the mechanism through which the R550C mutation acts is unclear, the authors suggest it might adversely affect the function of asparagine synthetase.

The researchers then analyzed gene-trap mice that contain an insertion in *Asns* that results in expression of *Asns* mRNA at ~20% of its normal levels. Homozygous *Asns* gene-trap mice had smaller brains and larger lateral ventricles than wild-type controls and showed impaired memory. Interestingly, the gene-trap mice had a milder phenotype than affected humans with mutations in *ASNS*, with no evidence of seizures, but the generation of *Asns*-null mice in future studies may help the further investigation of this microcephaly syndrome. —*MS*

IMMUNOLOGY

Mucous-mediated tolerance



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Most foods do not elicit an inflammatory response in the gut, but the mechanisms underlying oral tolerance are not entirely clear. Andrea Cerutti and his colleagues now report that MUC2, a glycosylated protein that is a major component of the mucous layer lining the gut, also regulates tolerance of dendritic cells (DCs) to oral antigens (*Science* doi:10.1126/science.1237910).

The authors showed that MUC2 dampens the production of inflammatory cytokines by DCs exposed to bacteria. Moreover, MUC2 induced increased expression of IL-10 and other immunosuppressive factors and enhanced regulatory T cell development *in vitro*. Compared with wild-type mice, Muc2-deficient mice had more proinflammatory T cell subsets in their small intestine lamina propria (SI-LP), higher production of proinflammatory cytokines from SI-LP DCs and lower levels of immunosuppressive cytokines from DCs and intestinal epithelial cells. Muc2-deficient mice showed higher antibody and T cell responses to antigens delivered orally compared with wild-type mice, but these immune responses could be reduced by coadministration of MUC2 and antigen.

The researchers then showed that glycosylated Muc2 interacts with DC surface galectin-3 and forms a complex with dectin-1 and the immunosuppressive receptor FcγRIIb. This interaction is required for the suppression of proinflammatory cytokine production by MUC2. These findings extend our understanding of the multifunctional role of MUC2 in the gut and the mechanisms regulating oral tolerance to ingested antigens. —*AF*

■ CANCER

Liver cancer progenitors

Premalignant lesions have been thought to lead to full-blown hepatocellular carcinoma. Research in mice now identifies tumor progenitor cells in these lesions, which are not yet fully malignant but can give rise to liver cancer in chronically damaged livers (*Cell* **155**, 384–396).

Guobin He and his colleagues isolated dispersed and aggregated hepatocytes from mouse models of liver cancer using collagenase digestion. After transplantation into mice with chronic liver damage, the aggregated, but not the dispersed, hepatocytes formed numerous liver tumors, suggesting that tumor progenitors might exist in these aggregates and give rise to tumors in the appropriate environment, as tumors were not found in organs other than the liver. Although the authors did not identify the cellular origin of the tumor progenitors, their analysis of the cells' markers and signaling pathways indicated that the progenitors may be derived from premalignant liver lesions, and such lesions are also present in premalignant human livers.

Mechanistically, the authors show that aside from transient interleukin-6 (IL-6) production by macrophages at early stages in liver cancer, autocrine IL-6 signaling, regulated by LIN28 expression, in tumor progenitors drives tumor growth. In dysplastic lesions in hepatic livers, IL-6 and LIN28 expression were increased compared with healthy livers. Thus, this study uncovers a major signaling circuit activated in premalignant liver cells that could be manipulated to prevent tumor progression. —*CP*

■ STEM CELLS

A reprogrammable rodent

Adult cells can be reprogrammed *in vivo* according to a recent report in *Nature* (**502**, 340–345).

Although reprogramming of somatic cells into induced pluripotent stem (iPS) cells can be achieved *in vitro* by ectopic expression of four factors (Oct4, Sox2, Klf4 and c-Myc), this had not been demonstrated *in vivo*.

Manuel Serrano and his colleagues now describe a mouse model in which administration of doxycycline induces the expression of these four reprogramming factors. Mice fed doxycycline developed teratomas that contain the three embryonic germ layers—mesoderm, endoderm and ectoderm—suggesting that the reprogrammed cells are fully pluripotent. Pluripotent cells were found in the stomach, intestine, pancreas, kidney and circulating in the blood of the reprogrammed mice. Reprogramming could also be induced in hematopoietic cells, as transplantation of bone marrow from the reprogrammed mice into wild-type hosts resulted in teratoma formation. The *in vivo*–generated iPS cells were more similar to embryonic stem cells than *in vitro*–generated iPS cells and could produce embryo-like structures after their injection into wild-type mice. Looking forward, these mice will provide a valuable tool to investigate reprogramming *in situ* and may point to novel strategies for promoting regeneration. —*KDS*

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