■ DISEASES OF THE NERVOUS SYSTEM

Neurons on the move

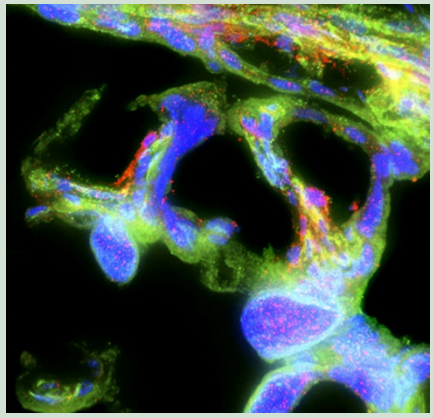
The intellectual disability and seizure disorder Börjeson-Forssman-Lehmann syndrome (BFLS) is linked to abnormal neuronal migration, according to a recent study (*Neuron* **78**, 986–993).

BFLS is caused by mutations in the gene that encodes the nuclear protein PHF6. When Chi Zhang *et al.* knocked down the expression of PHF6 in developing mouse brains using RNAi *in utero*, they observed reduced neuron migration to the outer layers of the cortex, leading the neurons to reside in an abnormal cortical location and become hyperexcitable. The expression of mutant versions of PHF6 that are found in individuals with BFLS could not rescue the abnormal migration phenotype, suggesting that dysfunctional neuronal migration causes the disorder in humans.

Zhang *et al.* found that PHF6 binds the transcription factor PAF1 and that knocking down PAF1 in developing mice also induces abnormal neuronal migration. In microarray experiments, the researchers found that expression of the transmembrane protein neuroglycan C was decreased in neurons with reduced expression of PHF6 compared with wild-type neurons and that reexpression of neuroglycan C could rescue cortical neuron migration in mice with PHF6 knockdown. Whether restoring neuronal migration via this mechanism could improve cognition in BFLS remains an open question. —*EC*

REPRODUCTIVE DISORDERS

Probing preeclampsia



Roger J. Bick & Brian J. Poindexter / UT-Houston Medical School / Science Source

A recent study investigating early events that occur during aberrant placentation in preeclampsia provides new insights into the pathogenesis of this syndrome (*J. Clin. Invest.* 123, 2862–2872).

During pregnancy, the differentiation and invasion into the uterus and its vasculature by a subset of placental cells called cytotrophoblasts is important for establishing maternal blood flow to the placenta. Previous studies have indicated that cytotrophoblasts fail to invade the uterus properly in preeclampsia. In their new work, Susan Fisher and her colleagues investigated the role of cytotrophoblasts in the pathogenesis of preeclampsia. They identified several genes that were differentially expressed in cultured cytotrophoblasts isolated from the placentas of women with preeclampsia compared with control cytotrophoblasts. Surprisingly, these expression changes were normalized after 48 h in culture, suggesting that the *in vivo* environment mediates the observed dysregulation of cytotrophoblast gene expression.

The researchers focused on one of the genes upregulated in preeclampsia cytotrophoblasts, *SEMA3B*, which encodes an antiangiogenic molecule. They found that adding SEMA3B to normal cytotrophoblasts could recapitulate some features of preeclampsia, including inhibition of cytotrophoblast invasion and increased cytotrophoblast apoptosis. They also showed that SEMA3B downregulates VEGF signaling through the PI3K–AKT and GSK3 pathways.

The finding that dysregulated gene expression in preeclampsia cytotrophoblasts is reversible suggests that it may be possible to develop therapeutic interventions for this condition. —*MS*

■ CANCER

miR-22 attacks on several fronts

Aberrant regulation of miRNAs and epigenetic abnormalities often occur in cancer. Two new studies show that miR-22 is an epigenetic modifier that promotes stemness and metastasis in cancer by targeting an enzyme that regulates DNA demethylation (*Cell* **154**, 1–14; *Cell Stem Cell* **13**, 87–101).

Su Jung Song *et al.* found that miR-22 was highly expressed in individuals with myelodysplastic syndrome and high-grade tumors, and that this correlated with poor survival. In mice, expression of miR-22 in the hematopoietic compartment increased stem cell maintenance and self-renewal, and this boost in hematopoiesis eventually caused hematological malignancy. Expression of the miRNA in mouse mammary glands promoted stemness, epithelial to mesenchymal transition and breast tumor development, as well as metastatic growth in a mouse model in which breast tumors spontaneously metastasize to the lung.

In both models, miR-22 blocked expression of TET family members, which induce DNA demethylation by converting 5-methylcytosine to 5-hydroxymethylcytosine. TET mutations are often found in human leukemias, and lack of Tet2 results in malignant transformation in mice; the two new studies suggest that regulation of TET2 by miR-22 may be also a key tumorigenic pathway in the hematological compartment. In breast tissue, miR-22 also promoted malignancy by suppressing the expression of TET2 and TET3. Moreover, miR-22 overexpression triggered metastasis through epigenetically silencing expression of the antimetastatic miR-200 family by targeting TET family members. The authors validated this link between miR-22 and the TET–miR-200 axis in human breast samples.

These findings emphasize the importance of antagonistic miRNA interactions and their influences on global epigenetic modifiers, which can result in tumor progression and metastasis, and also identify an oncogenic miR that acts in several tissues. Further work will be required to assess the therapeutic potential of targeting miR-22 to avert metastasis. —*CP*

■ CANCER METABOLISM

Metabolic silencing

A new study reveals striking patterns of epigenomic divergence related to metabolic alterations in gastrointestinal stromal tumors (GISTs) (*Cancer Discov.* **3**, 648–657).

Mitochondrial metabolic dysfunction is a common driver of GISTs, which frequently bear mutations in subunits of the Krebs cycle complex succinate dehydrogenase (SDH). Beyond the expected energetic and metabolic mayhem, it was unclear whether these driver mutations had other far-reaching effects in the tumors.

On the basis of prior evidence that metabolic alterations affect epigenetic modifications, the authors profiled the methylation