■ NEUROSCIENCE

A new genetic form of autism

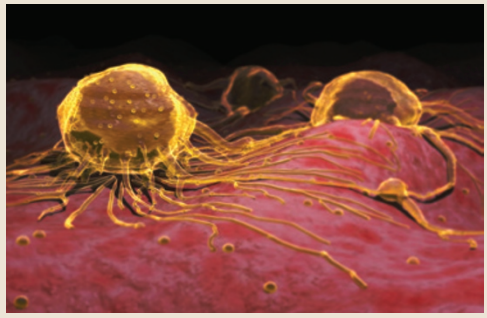
Loss of a protein involved in amino acid breakdown leads to a new form of autism with epilepsy, according to a paper published in *Science* (**338**, 394–397).

Gaia Novarino *et al.* performed whole-exome sequencing in families in which at least two siblings had autism, intellectual disability and abnormalities in their electroencephalogram. This allowed them to find inactivating mutations in the gene encoding branched chain ketoacid dehydrogenase kinase (BCKDK), an enzyme that regulates the catabolism of branched-chain amino acids, in the affected individuals.

In *Bckdk*-knockout mice, the authors observed behavioral abnormalities such as tremors and seizures but could not ascertain the molecular mechanism behind these deficits. But, crucially, the neurological phenotypes of the mice improved when they were fed a diet rich in branched-chain amino acids, raising the possibility that this form of autism may respond to dietary supplementation.—*JCL*

CANCER

Antitumor duality of ApoE



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An miRNA network drives melanoma metastasis by blocking the newly uncovered role of apolipoprotein E (ApoE) as a suppressor of angiogenesis and cell invasion (*Cell* doi:10.1016/j.cell.2012.10.028).

Nora Pencheva *et al.* screened metastatic cells generated from human melanoma cell lines to identify miRNAs that were specifically upregulated. Three candidates—miR-1908, miR-199a-3p and miR199a-5p—showed metastatic potential in mice, and their increased expression correlated with the metastatic potential of human primary melanomas. Their collective or individual expression enhanced metastatic invasion, endothelial cell recruitment and angiogenesis, suggesting that these miRNAs have both cell-autonomous and non–cell-autonomous tumor effects. The authors then found that this miRNA network converges on two common targets—ApoE and the heat shock factor DNAJA4—which could explain its dual role in melanoma. ApoE secreted by cancer cells blocks invasion and endothelial cell recruitment by binding the receptors LRP1 in tumor cells and LRP8 in endothelial cells. As DNAJA4 upregulates ApoE, the miRNAs have two routes of limiting ApoE secretion, thus fostering metastasis.

Although further research is needed to investigate whether increasing ApoE expression can decrease metastatic disease, these findings suggest a potential new target to blunt metastasis and angiogenesis in melanoma and perhaps also in other cancer types. —*CP*

■ CANCER

The importance of editing

A recent study shows that impaired miRNA editing leads to increased glioma cell migration and invasion (*J. Clin. Invest.* **122**, 4059–4076).

Yukti Choudhury *et al.* investigated the modification of the miR-376 cluster, which is known to be subject to RNA editing, in human glioma samples and glioma cell lines. There was less editing of miR-376 cluster transcripts in gliomas compared with normal brain tissue samples. High-grade gliomas showed higher amounts of the unedited form of the cluster miRNA miR-376a*, which correlated with the extent of tumor invasion.

Introduction of the unedited miR-376a* into glioma cells promoted cell invasion and migration, and injection of glioma cells expressing the unedited miRNA into mouse brains led to the development of more invasive tumors than cells expressing edited miR-376a*. The authors compared the genes regulated by the two forms of miR-376a* using microarray analyses, homing in on two candidates: *RAP2A*, a target of unedited miR-376a*, and *AMFR*, a target of edited miR-376a*. Downregulation of *RAP2A* and upregulation of *AMFR* led to increased migration of glioma cells, and these gene expression changes were also observed in human glioma samples and correlated with the expression of unedited miR-376a*.

These new findings highlight the importance of RNA editing in cancer and also indicate that unedited miR-376a* might be a therapeutic target in glioblastoma.—*MS*

■ IMMUNOLOGY

Beyond tolerance

Regulatory T (T_{reg}) cells suppress conventional T cell responses, and, in their absence, mice and humans develop autoimmune diseases. Yet, T_{reg} cells have also been shown to promote protective responses against pathogens. Sebastian Amigorena *et al.* now report that T_{reg} cells help focus the $CD8^+$ T cell response to nonself antigens by inhibiting low-avidity T cell responses (*Science* **338**, 532–536).

In mice lacking T_{reg} cells, the researchers found that immunization with a nonself antigen increased the number of antigen-specific $CD8^+$ T cells and the frequency of $CD8^+$ T cells recognizing the antigen with low avidity. However, these T cells did not promote long-lived memory.

Using two ovalbumin (OVA) peptide variants that are recognized with different affinities by the OT-I T cell receptor, the authors then showed that immunization with dendritic cells (DCs) loaded with the lower-affinity OVA peptide induced little expansion of OT-I T cells in wild-type mice, but marked expansion in T_{reg} cell–depleted mice. They attributed the expansion of OT-I T cells to increased production by DCs of the chemokines CCL3 and CCL4, which is suppressed by T_{reg} cells. OT-I T cell recognition of the high-affinity peptide induced high amounts of these cytokines that were not affected by T_{reg} cell depletion. The researchers further showed that interactions of DCs loaded with the low-affinity peptide and T cells were stabilized in T_{reg} cell–depleted mice in a CCL3-, CCL4- and/or CCL5-dependent manner.

When the authors infected T_{reg} cell–depleted mice with *Listeria monocytogenes,* although the frequency of low-avidity T cells increased during primary infection, these cells were less able to control the bacterial burden upon secondary infection than T cells in T_{reg} cell–replete mice. These results suggest that T_{reg} cells are required for the generation of functional T cell memory and a focused, high-avidity $CD8^+$ T cell response against pathogens. —*AF*

■ AUTOIMMUNITY

NET loss in lupus

Disease pathology is worsened in lupus-prone mice deficient in the enzyme NADPH oxidase (Nox2), suggests a study published in *Science Translational Medicine* (doi:10.1126/scitranslmed.3004801).

Autoantibodies directed at self antigens are