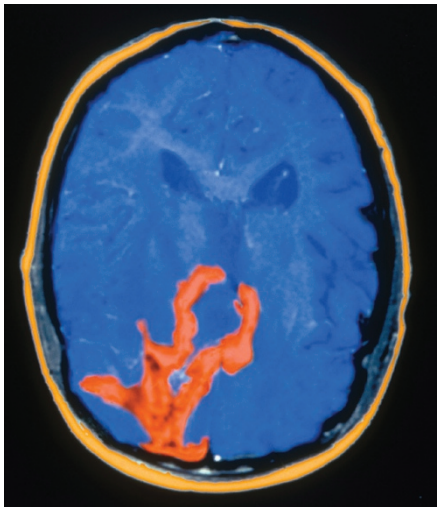
implicates the receptor tyrosine kinase EphA3 in GBM progression and highlights a new potential therapeutic approach (*Cancer Cell* **23**, 238–248).

Brian W. Day and his colleagues showed that EphA3 was significantly overexpressed in about 40% of human glioma samples they studied. They associated elevated EphA3 expression with poor survival of patients afflicted with the mesenchymal subtype of GBM, an undifferentiated and particularly aggressive form of the cancer.



Gregory G. Dimijian, M.D. / Science Source

As GBM development is primarily driven by undifferentiated progenitor or cancer stem cells that confer self-renewal abilities and drug resistance, the authors investigated whether EphA3 affects the differentiation of GBM cells. By depleting EphA3 using RNAi, they ascertained that EphA3 promotes an undifferentiated state in GBM cells. Maintenance of the undifferentiated cell state hinges on an EphA3 kinase–independent function that dampens signaling through the Erk–MAPK cascade, which would otherwise reduce proliferation and promote differentiation.

Adding a therapeutic facet to their study, the authors then showed that an EphA3-specific antibody effectively depleted EphA3 and reduced proliferation and tumorsphere-forming potential in cultured GBM cells. Moreover, when endowed with a radioactive moiety, the antibody led to the regression of xenografted GBM tumors in mice, suggesting that such a strategy may hold promise for a subgroup of patients with GBM.—*BB*

■ NEURODEGENERATION

A repeat offense

Expansion of a six-nucleotide motif (GGGGCC) in the *C9orf72* gene is one of the major causes of the neurodegenerative diseases frontotemporal dementia (FTD) and amyotropic lateral sclerosis (ALS). Now, Peter Ash *et al.* and Kohji Mori *et al.* have found that alternative translation initiated from the nucleotide expansion leads to the formation and aggregation of polydipeptides within the central nervous system of patients with the expansion (*Neuron* **77**, 1–8; *Science* doi:10.1126/science.1232927).

Both groups generated antibodies to the polydipeptides they hypothesized would be generated from translation of the nucleotide expansion. Mori *et al.* showed that they could observe alternative translation from the nucleotide expansion when they transfected constructs containing the repeat region into a cell line. Both groups observed dipeptide aggregates within the brains of patients with FTD and ALS who had the nucleotide expansion, but they did not see any aggregates in patients who did not have the expansion. Ash *et al.* did not observe any dipeptide aggregates in patients with other nucleotide-repeat diseases. The findings suggest that these polydipeptides could contribute to disease in patients carrying *C9Orf72* repeat expansions.—*EC*

■ HEPATITIS B

Negative regulation by NK cells

T cell responses in the liver are tightly regulated to limit damage to this important tissue, but mechanisms to ensure T cell tolerance in this setting can also be manipulated by pathogens. A recent study provides insights into how natural killer (NK) cells can downregulate T cell responses in chronic hepatitis B virus (HBV) infection (*J. Exp. Med.* **210**, 99–114).

HBV-specific $CD8^+$ T cells required for viral control have previously been found to be depleted in patients chronically infected with HBV. In cultured cells from HBV-infected patients, Dimitra Peppa *et al.* found that depletion of NK cells increased the number of HBV-specific $CD8^+$ T cells. They showed that the NK cells directly come into contact with the $CD8^+$ T cells and induce their apoptosis.

Mechanistically speaking, intrahepatic $CD8^+$ T cells that had been exposed to HBV upregulated their expression of a death receptor, TRAIL-R2, making them susceptible to NK cell–mediated deletion. Blocking the TRAIL pathway *in vitro* partly rescued HBV-specific $CD8^+$ T cells, but to a lesser extent than deleting NK cells, suggesting that NK cells may have additional pathways to downregulate T cells.—*MS*

Written by Benjamin Boettner, Eva Chmielnicki, Juan Carlos López, Carolina Pola and Meera Swami

New from NPG

Identification of a candidate therapeutic autophagy-inducing peptide
Shoji-Kawata, S. *et al. Nature* doi:10.1038/nature11866 (30 January).
This study describes a potent inducer of autophagy, Tat-beclin1, which may have therapeutic potential. The peptide decreased the replication of a number of infectious agents *in vitro*, and reduced the mortality of mice infected with chikungunya or West Nile virus.

Relapse-specific mutations in NT5C2 in childhood acute lymphoblastic leukemia
Meyer, J.A. *et al. Nat. Genet.* doi:10.1038/ng.2558 (3 February).
By sequencing matched childhood acute lymphoblastic leukemia bone marrow samples at diagnosis and relapse, the authors identified mutations in the nucleotidase gene *NT5C2* in relapse samples. The cognate mutant proteins showed increased enzymatic activity and resistance to nucleoside analog therapies.

Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues
Bernink, J.H. *et al. Nat. Immunol.* doi:10.1038/ni.2534 (20 January).
This paper identifies a distinct innate lymphoid cell (ILC) subset in humans, which the authors call 'ILC1' cells. ILC1 cells were found in higher numbers in inflamed intestinal tissue from individuals with Crohn's disease, suggesting these cells may have a role in gut inflammation.

A recurring motif for antibody recognition of the receptor-binding site of influenza hemagglutinin
Xu, R. *et al. Nat. Struct. Mol. Biol.* doi:10.1038/nsmb.2500 (10 February).
The authors report the crystal structures from three human neutralizing antibodies to the pandemic H2N2 influenza virus complexed with H2 hemagglutinin (HA), providing new insights into the interactions between neutralizing antibodies and HA that may help design more effective inhibitors to influenza virus entry.

Epigenetic control of female puberty
Lomniczi, A. *et al. Nat. Neurosci.* doi:10.1038/nn.3319 (27 January).
The authors identify an epigenetic mechanism regulating the timing of female puberty in rats. This involves the binding of the Polycomb group protein EED to the promoter of *Kiss*, a key puberty-activating gene, thus repressing Kiss expression prior to puberty.