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INSIDE LAB INVEST

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Drinking like a fish?

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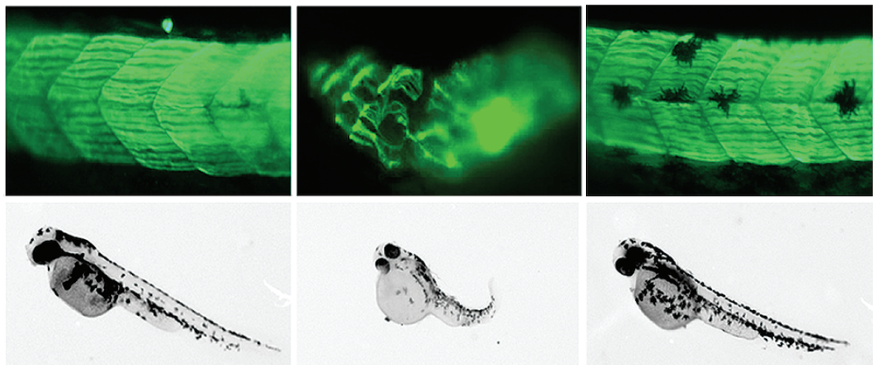

Ethanol consumption by pregnant women can cause neurodevelopmental defects, craniofacial dysmorphism, and growth retardation, collectively referred to as fetal alcohol spectrum defects (FASD). Despite extensive research, mechanisms causing FASD have been poorly described. In this issue, Li *et al* provide evidence that ethanol disrupts embryogenesis via inhibition of Shh cholesterol esterization. Using a zebrafish model, Li *et al* found that ethanol-treated embryos developed defects similar to those in human FASD. Similar developmental defects were induced by inhibitors of Shh signaling or cholesterol synthesis, suggesting a shared developmental mechanism for all three perturbations. Indeed, Shh transcription activity was reduced in ethanol-treated embryos, and addition of exogenous cholesterol was able to prevent ethanol-induced developmental defects. Thus, this study is the first to provide a mechanism for FASD: ethanol disrupts Shh cholesterol esterization, in turn reducing Shh signaling. The implications for prevention of birth defects cannot be overstated.
Le Shen, MD., PhD, The University of Chicago, Chicago IL

Cell death in nasal-type NK/T-cell lymphoma: the killing from within

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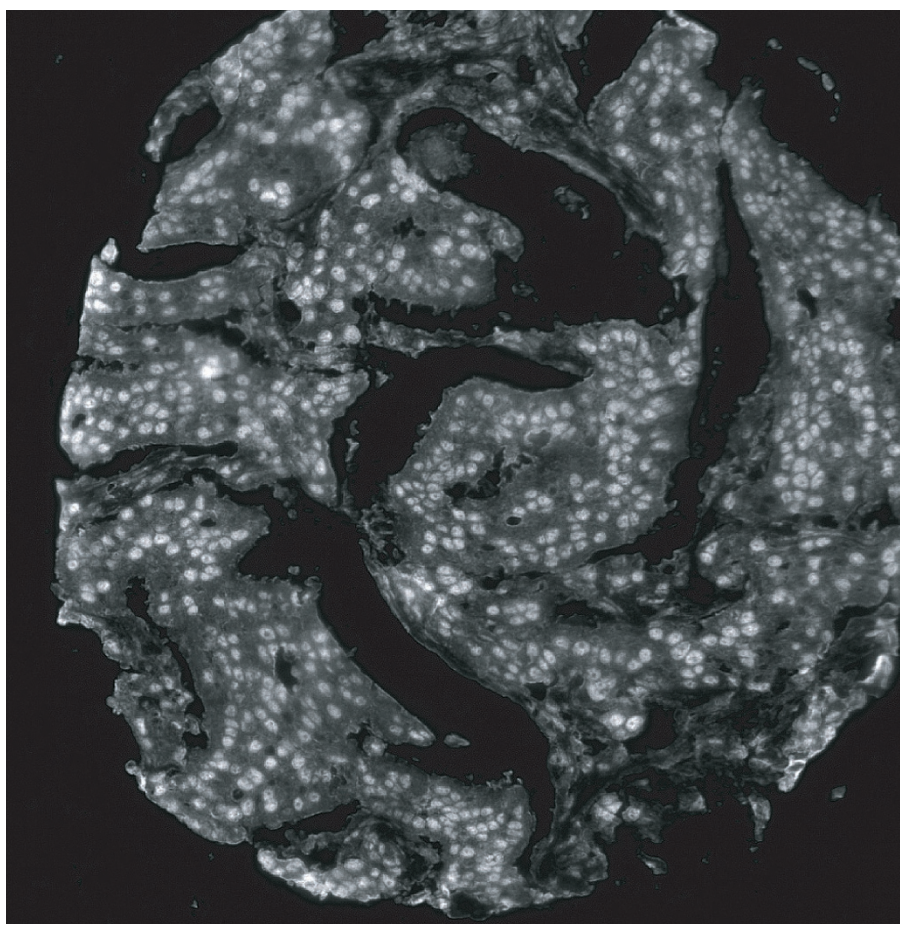
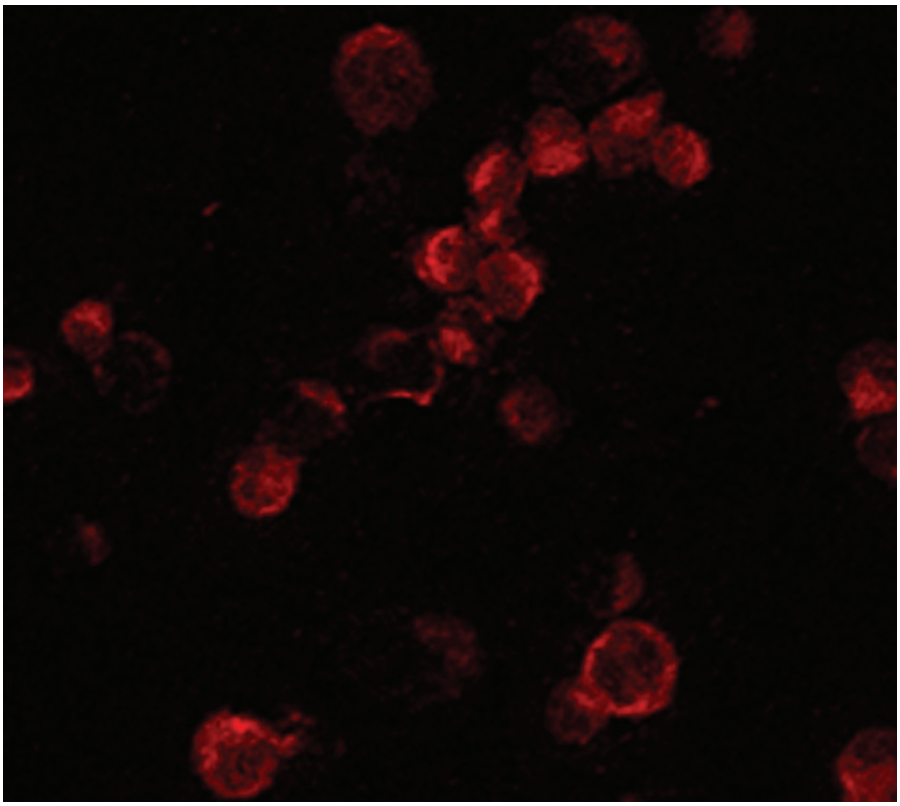


Nasal-type NK/T-cell lymphoma (NKTL) is an aggressive neoplasm of cytotoxic cells associated with Epstein-Barr virus. The tumor cells exhibit spontaneous apoptosis, and extensive coagulative tumor necrosis is common. Granzyme B, a protease generally confined within lytic granules in the cytoplasm of normal NK and cytotoxic T lymphocytes, is also expressed in NKTL. In this issue, Ko *et al* investigated the role of granzyme B in the apoptosis and necrosis of NKTL and show that the cell death in these tumors may be induced by granzyme B leakage. Using lymphoma tissues and cell lines, the authors provide data to suggest that the neoplastic cells may undergo self-induced death through the release of granzyme B within the cell in which it lies. Although other mechanisms may play a role in the induction of necrosis and apoptosis in NKTL, the results of this study provide a novel explanation for the massive cell death that is commonly seen in these lymphomas. *RCB*



Validation of Met immunohistochemistry in breast cancer

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The receptor for hepatocyte growth factor (HGF) is Met. Binding of HGF to this receptor activates intracellular signaling pathways responsible for cellular proliferation, motility and branching morphogenesis, and cellular invasion. Immunohistochemical expression of Met at high levels has been associated with a poor clinical prognosis in several epithelial cancers, including breast, gastric, cervical, and head and neck carcinomas. However, there are two problems in making such assessments: the heterogeneous expression of Met within tumors and the reproducibility of the immunological reaction between antibody and protein epitopes. Moreover, poorly differentiated breast carcinoma cells may cleave the cytoplasmic tail of the Met receptor, generating a free cytoplasmic peptide fragment that may translocate to the cell nucleus, confounding morphological assessment of Met expression. In this issue, Pozner-Moulis *et al*. examined the antibody reproducibility for many of the Met-directed commercial antibodies and obtained highly variable results. A reproducible Met antibody directed toward the cytoplasmic COOH terminal was identified and used to analyze a cohort of 640 breast carcinomas via tissue microarray. Using automated quantitative analysis, nuclear expression of Met was found to be predictive of worse 5-year clinical outcomes. This study points out the critical need to validate antibodies used on tumor samples to obtain prognostic information, and the importance of paying attention to the cellular distribution of immunoreactivity. The study also raises the possibility that expression of Met within the cell nucleus may be a marker of tumor aggressiveness, independent of traditional biomarkers such as Her2, ER, and PR. *JC*

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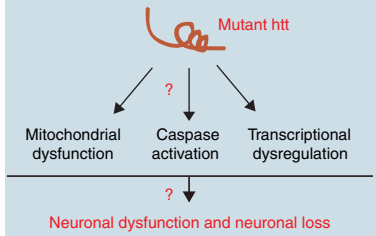
Cell death in Huntington disease
Huntington disease (HD), an inherited neurodegenerative disorder results from the expression of mutant huntingtin (htt) protein. The mechanisms by which the mutant htt protein contributes to HD remain unclear. In *Nature Chemical Biology*, researchers recently reported the identification of 29 novel selective inhibitors of cell death in mutant htt-expressing cells. Four of these compounds were active in diverse HD models, suggesting a role for cell death in HD. These compounds are potential drug leads and should be valuable tools for further elucidating the pathology of HD.
Nature Chemical Biology, 3, 99–100, 2007; doi:10.1038/nchembio852



Stem cell origin of cancer In embryonic stem cells, Polycomb group proteins reversibly repress genes required for differentiation. A recent article in *Nature Genetics* reported that stem cell Polycomb group targets are up to 12 times more likely than non-targets to have cancer-specific promoter DNA hypermethylation. This discovery supports a stem cell origin of cancer in which reversible gene repression is replaced by permanent silencing, which locks the cell into a state of self-renewal and predisposes it to malignant transformation.
Nature Genetics, 39, 157–158 2007; doi:10.1038/ng1941

Susceptibility variant for Crohn disease
A genome-wide association study of non-synonymous SNPs identified a Crohn disease association of marker rs2241880, a coding SNP in the ATG16L1 gene. This gene encodes a protein in the autophagosome pathway that processes intracellular bacteria. The rs2241880 marker was found to carry virtually all the disease risk exerted by the *ATG16L1* locus. rs2241880 had a significant interaction, with respect to Crohn disease risk, with *CARD15* susceptibility variants and lacked an association with ulcerative colitis, which suggests that the underlying biological process may be disease specific.
Nature Genetics, 39, 207–211 2007; doi:10.1038/ng1954