

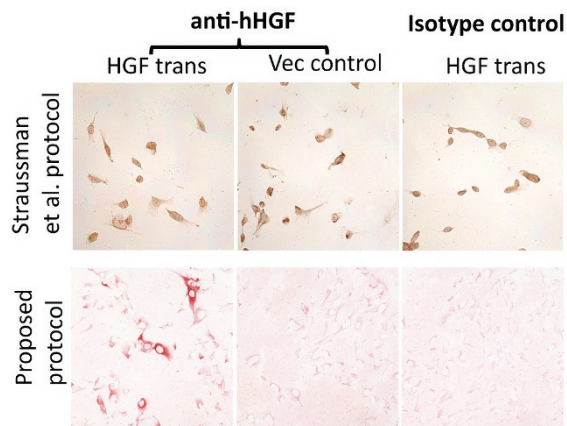
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MODERN PATHOLOGY

The challenges of biomarker development

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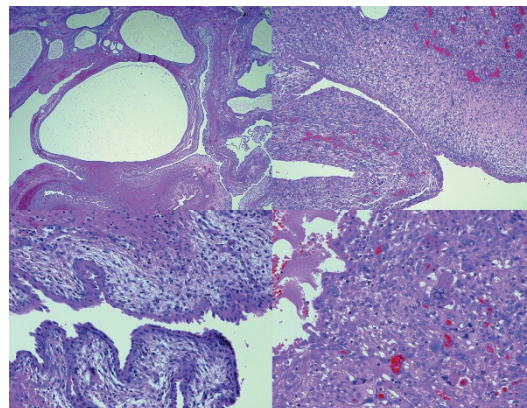


Several studies have suggested that expression of stromal hepatocyte growth factor (HGF) promotes resistance in melanoma to BRAF inhibitors. Because HGF can be readily detected by immunohistochemistry, validation of such a biomarker could be helpful for clinical prediction and management. Lezcano *et al* performed very meticulous studies using multiple orthogonal detection methods to ensure detection of stromal HGF with appropriate sensitivity and specificity. Examination of a carefully curated set of retrospective clinical samples with known outcome to BRAF inhibitors showed that HGF expression had no significant predictive power. The authors use this negative outcome to convey the sad truth that, despite the many thousands of studies purporting usefulness of clinical biomarkers, only a handful ever enter routine clinical practice—a sobering reality for investigators. Their clarion call for vastly improved adherence to the criteria established to validate biomarkers, such as REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies), should not be ignored.

DICER1 mutations in childhood cystic nephroma

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Doros *et al* propose that cystic nephroma is similar to pleuropulmonary blastoma, with analogous morphologic spectra and risk of malignant transformation. A familial association between these two neoplasms has been described. Germline mutation of *DICER1*, encoding a major microRNA processing enzyme, has been implicated in pleuropulmonary blastoma familial tumor predisposition syndrome. These are

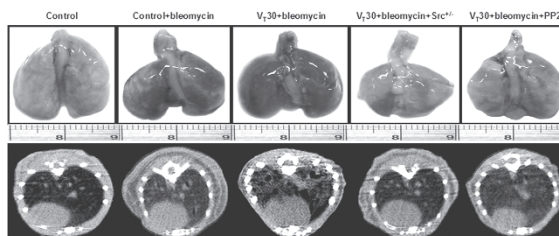


usually hotspot mutations in the RNase IIIb domain and cause a loss of function. Neoplastic development seems to follow the Knudson two-hit scheme, with loss of heterozygosity at the nonmutated allele. The authors found mutations in *DICER1* in 90% of childhood cystic nephromas. Analysis of a subset with sarcomatous transformation also showed *DICER1* mutations suggesting an association with cystic nephroma; however, further study is needed, given reports of *DICER1* mutations in unrelated neoplasms, such as Sertoli–Leydig tumors of the ovary.

Laboratory Investigation

Src pathway mediates epithelial damage by mechanical ventilation

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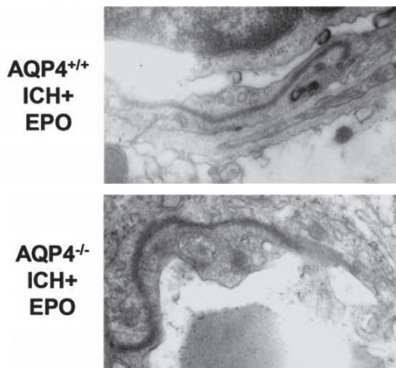


Acute respiratory distress syndrome (ARDS) often requires mechanical ventilation, but this treatment can compromise pulmonary epithelium. Li and colleagues show that mechanical ventilation induces tidal-volume stretches that trigger epithelial-to-mesenchymal transition (EMT) and fibrosis. During this process, a milieu of proinflammatory cytokines helps induce collagen production. In a mouse model in which acute lung injury was simulated by bleomycin, Src signaling was induced with mechanical ventilation. Mice genetically deficient in Src showed less

lung damage, and pharmacologic inhibition of the Src pathway attenuated damage. The Src pathway appears to mediate the fibroproliferative phase of ARDS in part by facilitating epithelial cell death and stimulating EMT. This study suggests therapeutic maneuvers that could limit the damage induced by necessary mechanical ventilation in the setting of ARDS, buying the time needed to promote recovery.

Protection of the BBB with erythropoietin mediated by aquaporin-4

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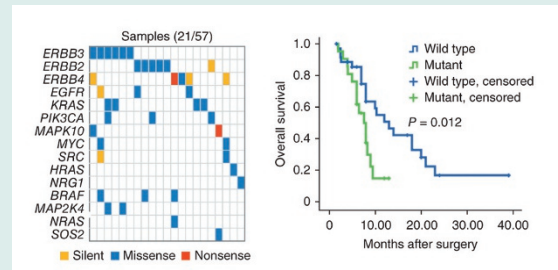
Intracerebral hemorrhage can lead to disruption of the blood–brain barrier (BBB). The neuroprotective effects of erythropoietin have been well described in this setting and others. Chu *et al* demonstrated in a mouse model that the erythropoietin receptor is expressed around the hematoma and that erythropoietin treatment increased the levels of both its cognate receptor and aquaporin-4 (AQP4), a water channel that helps to maintain BBB integrity. Using a mouse null for AQP4 expression, the authors found that this protein mediates, at least in part, the protective effects of erythropoietin treatment. The JNK and p38-MAPK pathways may mediate receptor signaling for additional AQP4 expression. The effects of erythropoietin treatment included reduction of both brain edema and BBB permeability. This was associated with increased expression of tight-junction proteins.

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Mutations in the ErbB pathway in gallbladder carcinoma

In a study reported in *Nature Genetics*, Li *et al* examined gallbladder carcinoma using both exome sequencing and focused deep sequencing of cancer genes. In this rare, aggressive, and poorly understood neoplasm, the authors found *TP53* mutations in close to half of all the cases and activating mutations in *KRAS* in about 8%. In 37% of the cases, the ERBB pathway was mutated at multiple points in the pathway, including *ERBB3*, *ERBB2*, *ERBB4*, *EGFR*, and additional downstream components of the pathway. Most of these mutations were mutually exclusive. Mutation in the ERBB pathway correlated with tumor occurrence at the neck of the gallbladder. The presence of ERBB pathway aberrations was associated with a poorer clinical outcome. The genetic findings contrast with those for the chromatin-remodeling genes *BAP1*, *ARID1A*, and *PBRM1* described in cholangiocarcinoma, despite the fact that both tumors arise in the biliary epithelium.

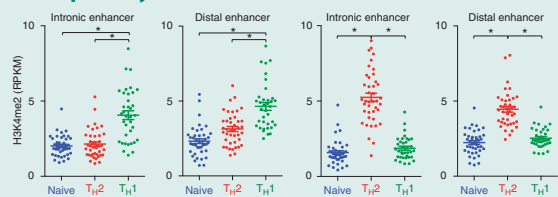
Nature Genetics 2014;46:872–876; doi:10.1038/ng.3030



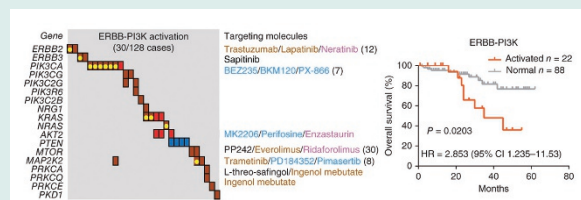
T-cell epigenomics and asthma susceptibility

A characteristic feature of asthma is overproduction of type 2 cytokines by memory CD4⁺ T cells. As described in *Nature Immunology*, Seumois and colleagues isolated T cells from the peripheral blood of both healthy and asthmatic individuals. They systematically profiled the genomes of naive and memory CD4⁺ T cells—T helper types 1 and 2 (Th1 and Th2)—for histone modifications, termed “marks,” and focused on modifications of enhancers involved in T-cell development and function. Distinct differences were seen in T cells from asthmatic patients and those from normal controls. Enhancers showing a mark at histone H3 Lys4 dimethyl were enriched in Th2 cells with asthma-associated single-nucleotide polymorphisms. These results provide a very novel look at the functional genomics of asthma and underscore the importance of Th2 cells in the pathogenesis of this disease.

Nature Immunology 2014;15:777–788; doi:10.1038/ni.2937



Nasopharyngeal genomic features revealed



As recently described in *Nature Genetics*, Lin *et al* explored the genomic landscape of nasopharyngeal carcinoma, a rare malignancy with higher prevalence in southern China, southeast Asia, and northern Africa. Epidemiologic studies point to genetic susceptibility, Epstein–Barr virus infection, and chemical carcinogens as etiologic factors. Analysis of 128 cases via exome and targeted deep sequencing revealed a molecular signature comprising nine significantly mutated genes primarily in pathways governing chromatin modification, G1/S transition, and the ERBB-PI3K pathway. Using integrative genomics, the authors detected aberrations in additional members of the ERBB-PI3K pathway—a total of 18 different genes. Mutation or copy-number variation of genes in this pathway portended a poorer clinical outcome, but potential targeted treatments were conceivable in a significant subset of cases. Lin *et al* also noted accumulation of mutations in adhesion, differentiation, and autophagy pathways, thus informing both the pathobiology and potential treatment approaches.

Nature Genetics 2014;46:866–871; doi:10.1038/ng.3006