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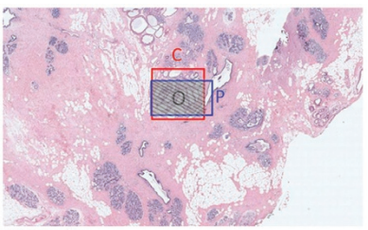
MODERN PATHOLOGY

Region of interest identification in breast pathology

See page 1004

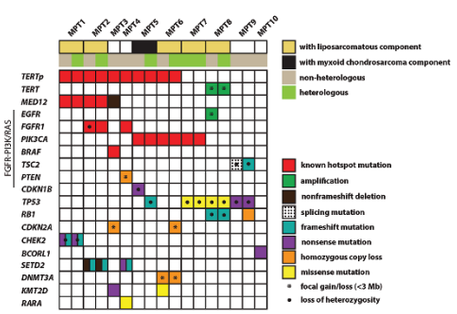


86% Overlap
Participant Diagnosis: Atypia

Nagarkar *et al* assessed 1,972 individual breast biopsy diagnoses, cataloging features such as age and gender of pathologists. A statistically positive trend in diagnostic agreement was noted in the aggregate data for all cases with overlapping diagnostic regions of interest (ROIs). Where a consensus reference standard was used to identify the ROI assessed, diagnostic agreement between pathologists was greater. The skill in identifying potential diagnostic features has been shown to be critical, with the largest incremental increase in diagnostic concordance shown between groups with no observed overlap in ROIs and the next lowest category (1–33%). Diagnostic agreement where there was no ROI overlap might have been due to both standard issues associated with diagnostic accuracy and technical limitations. The authors conclude that identification of an ROI on a histopathology slide is a significant predictor of diagnostic accuracy.

Genomic profiling of malignant phyllodes tumors

See page 1012

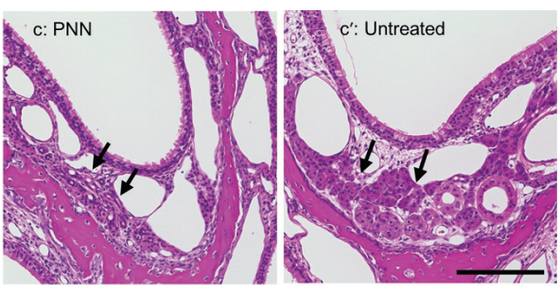


Liu *et al* set out to identify the molecular landscape of the rare and poorly understood malignant phyllodes tumors of the breast by sequencing 510 cancer-related genes in 10 tumors. Recurrently mutated genes included *FGFR1* (2/10) and *PIK3CA* (3/10), but together FGFR/EGFR PI-3 kinase and RAS pathway mutations were identified in 8/10 tumors, and promoter and amplification mutations in *TERT* were identified in 7/10 malignant phyllodes. The *TERT* promoter hotspot mutations were identified specifically in borderline phyllodes as opposed to benign tumors. The authors found that malignant phyllodes tumors exhibiting the *TERT* alterations had fewer large-scale chromosomal alterations than malignant phyllodes tumors that did not. Two activating mutations in FGFR1, not previously described in phyllodes tumor, were also shown at N546K and K656E. In aggregate, these findings suggest potential new targets for therapeutics in these tumors.

LABORATORY INVESTIGATION

Mucosal denervation for allergic rhinitis

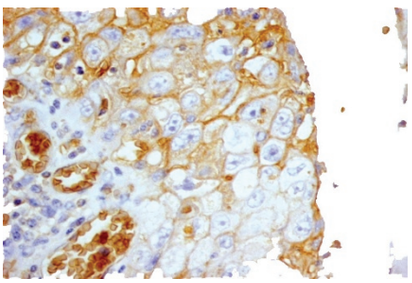
See page 981

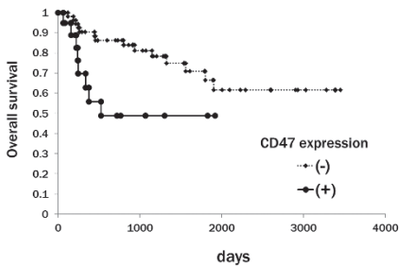


The posterior nasal nerve is the primary pathway for sympathetic, parasympathetic, and stimulatory signals feeding the nasal respiratory mucosa. Following the development of a rat model of posterior nasal neurectomy (PNN), Nishijima and his group sought to observe the impact of PNN-induced denervation of the nasal mucosa on allergic rhinitis. The model was characterized by rats showing depletion of nerve fibers, choline acetyltransferase, and neuropeptides in the nasal respiratory mucosa. Tests of the mechanisms by which PNN reduced nasal secretion revealed that PNN abrogates acetylcholine synthesis but not acetylcholine receptor function and expression. They found that allergic provocation in the PNN model reduced nasal secretion without affecting sensitization-based allergic symptoms or cytokine expression in the mucosa. The model is believed to provide a tool for further investigation into the role of the nasal nervous system in allergic rhinitis.

CD47 and TAM subsets in OSCC

See page 994





Traditionally, macrophages are broadly considered as having two subsets—M1 and M2—with the former being immunostimulatory and the latter being immunoregulatory or largely suppressive. Investigations of tumor-associated macrophages (TAMs) and CD47 expression on tumor cells is generally considered a 'don't eat me' signal that inhibits the phagocytic activity of macrophages. Sakakura *et al* used immunohistochemistry to assess $CD68^+$ and $CD163^+$ macrophage subsets in terms of infiltration into tumor tissue in conjunction with CD47 expression on cancer cells, directly correlating their results with clinicopathological parameters or prognoses. They demonstrated a relationship between survival and expression of CD47, CD68, and CD163 in squamous cell carcinoma of the head and neck (SCCHN), with expression of CD47 in the patient tumor tissue, or the infiltration of $CD68^+$ pan-macrophages into the SCCHN tissue correlating with poor overall survival. Infiltration of M2 (immunoregulatory or induced by macrophage colony-stimulating factor and interleukin-10) macrophages was shown to be an independent prognostic factor for both overall and progression-free survival.

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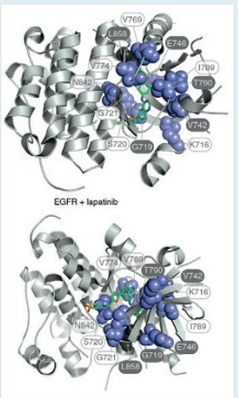
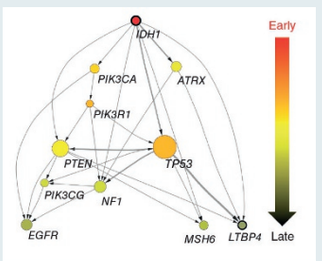
3D model of functional mutations



Niu *et al* set out to develop a computational model that would systematically identify three-dimensional (3D) spatial clusters or hotspots of mutations within human cancers. Mutations were identified in 369 genes, including *TP53*, *VHL*, and *EGFR*, all of which mapped within clusters that had potential functional implications. VHL mapped with 95% variant clusters specific to kidney renal clear cell carcinoma, whereas mutations in TP53, PIK3R1, and KRAS did not associate with a specific cancer type. EGFR was isolated for the purposes of validation of the HotSpot3D model using reverse-phase protein assay expression data because of its high number of protein variants across multiple patient samples. The authors' assay showed that EGFR with p.Thr790Met variant was resistant to gefitinib, consistent with previous reports. The team envisions using HotSpot3D in the discovery of relationships among variants in population as well as germline studies to see *de novo* mutations that play a role in many diseases.

Nature Genetics 2016;48:827–837; doi:10.1038/ng.3586

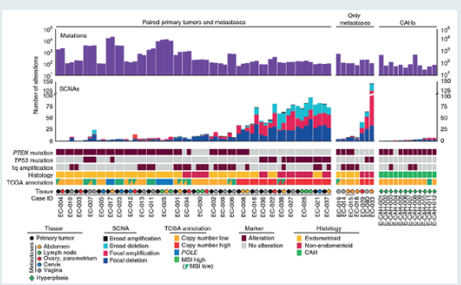
How glioblastoma evolves with therapeutic selection



Analysis of genomic and transcriptomic data from 114 glioblastoma (GBM) patients revealed that in 63% of the patients in this study there were expression-based subtype changes and a highly branched evolutionary pattern associated with temozolomide treatment. The authors were able to use the data to estimate evolutionary rate to predict relapse-associated clones years before diagnosis. The researchers illustrated the mutational landscape of recurrent GBM based on clinical and genetic profiles of patients and the correlation between different features. They produced data demonstrating cross-sectional integration of longitudinal DNA changes suggesting the order in which certain mutations probably occur, from *IDH1* through *PIK3* and out to *LTBP4*. Because *LTBP4* was mutated in 11% of relapsed tumors and it encodes a protein that binds to transforming growth factor-β, which is involved in cell proliferation and apoptosis, the data support the model for future work to learn more about the branching processes behind GBM evolution and treatment.

Nature Genetics 2016;48:768–776; doi:10.1038/ng.3590

The genomic evolution of endometrial carcinoma



Tumor progression proceeds with selective pressure molding cancer cell populations with both genetic and epigenetic variation. Analysis of genome-wide changes through endometrial cancer progression showed heterogeneity between biopsies of paired primary tumor and metastases. *NRIP1* mutations were identified in 12.5% of tumors. NRIP1 is an obligate cofactor of the estrogen receptor (ER), correlating with existing data associating *NRIP1* alterations with ER+ breast cancer. Gibson *et al* used their data to determine the sequence in which mutations probably occurred in the evolution of endometrial carcinoma, by looking at likely drivers of primary oncogenesis such as *PIK3CA*, *PTEN*, and *TP53* as opposed to mutations in *ARID1A*, frequently subclonal and thought to be altered later in development. Because convergent evolution was not the only cause of *ARID1A* and other mechanisms leading to its inactivation, the authors' hypothesis was that these might converge to generate phenotypic homogeneity. Further analysis is necessary for more resolution and clarification of this data.

Nature Genetics 2016;48:848–855; doi:10.1038/ng.3602

Emma Judson contributed to these reviews.