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Modern Pathology

A gene expression panel identifies origin site of neuroendocrine tumors

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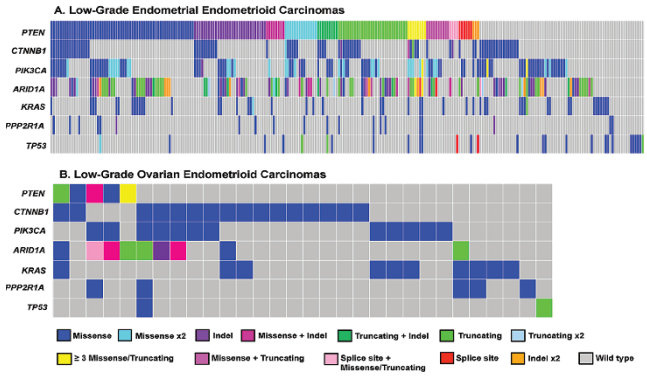

Neuroendocrine tumors (NETs) are often readily diagnosed, but the site of origin may be challenging to determine. Knowing the site of origin is important for grading and staging, clinical management, and application of targeted therapies. Kerr *et al* addressed this conundrum by analyzing both metastatic and primary tumors of gastrointestinal, pulmonary, Merkel cell, pancreatic, pheochromocytoma, and medullary thyroid types using quantitative reverse transcription–PCR with a previously validated 92-gene panel. The specimens were enriched to 80–90% tumor nuclei content via manual or laser-capture microdissection. Overall, 99% of tumors were correctly classified, and 95% were correctly assigned to the known site of origin previously established by expert clinicopathologic diagnosis. Not surprisingly, identification was more accurate in well-differentiated NETs than in poorly differentiated cases. The tumors consisted of a mixture of primary and metastatic foci, and the test performed well in the latter setting.

Differing spectra of *CTNNB1* and *PTEN* mutations in gynecologic tumors

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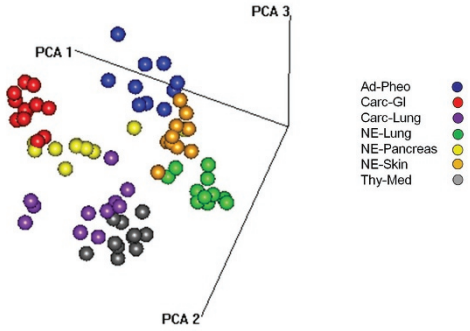
Low-grade endometrial endometrioid carcinoma (EEC) and ovarian endometrioid carcinomas (OEC) have similar morphologic characteristics and shared molecular derangements. McConechy *et al* examined cohorts of these two tumors and found that *PTEN* mutations are more prevalent in EEC whereas *CTNNB1* mutations are more prevalent in OEC. The prevalence of *PTEN*, however, was similar in both tumors. *ARID1A*, *KRAS*, *PP2R1A*, and *TP53* were relatively common in both tumors, with similar distributions. These differences suggest dissimilarities in the microenvironments in which EEC and OEC arise, thus suggesting insights into pathogenesis, despite the equivalent histologic findings. In addition, these differences may eventually lead to divergent rational therapeutic approaches in upcoming clinical trials.



Laboratory Investigation

A quantitative fluorescence-based method to assess Ki-67 score in mammary carcinoma

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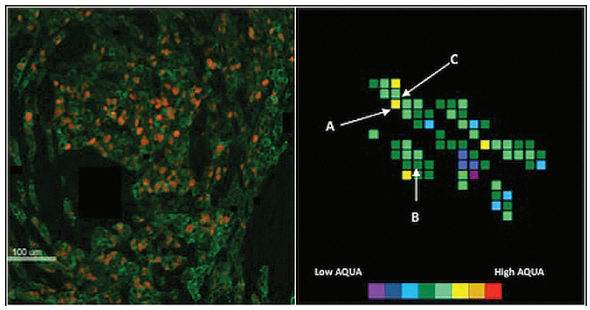

Previous studies have suggested an association of proliferation indexes derived using Ki-67 markers with response to treatment for breast cancer. However, there is no consensus on a method for assessing Ki-67. Using a well-characterized immunofluorescence platform, Brown and colleagues examined a cohort of 105 pretreatment core-needle biopsy specimens for Ki-67 reactivity. The number of fields of view examined ranged from 5 to 115, with a mean of 30. The results were reported as percentage of positive tumor nuclei and automated quantitative analysis (AQUA) score. The latter uses anti-cytokeratin antibodies to identify tumor cells and 4′6-diamidino-2-phenylindol to identify the nuclei within tumor cells. The Ki-67 nuclear intensity was determined within tumor nuclei and divided by total

tumor nuclei area to obtain the AQUA score. Full multivariate analysis showed that both the mean and maximum Ki-67 AQUA scores in a particular field of view were significant independent predictors of pathologic complete response to neoadjuvant chemotherapy, as was percentage of positive tumor nuclei. This rigorous and objective assessment of Ki-67 expression confirms that it is an important variable for predicting therapeutic outcome.

Loss of inflammatory pathway expression correlates with advanced HCC stage and poor differentiation

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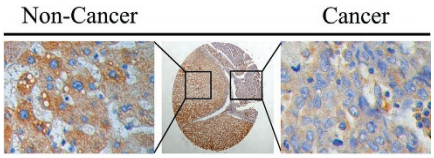

There are intracellular protein heterocomplexes called inflammasomes that serve as staging areas for the maturation and secretion of the key proinflammatory cytokine interleukins, IL-1β and IL-18. NLRP3 is perhaps the best characterized inflammasome and serves to incite an inflammatory response upon detection of various insults to the host and thus generally plays a protective role for the host. Wei *et al* demonstrate loss of this inflammasome in hepatocellular carcinoma (HCC) relative to adjacent normal liver. They assessed this by both immunohistochemistry and quantitative reverse transcription–PCR for multiple components of this complex and IL-1β. Reduced expression was also seen in cirrhosis, and in HCC was correlated with both advanced tumor stage and poor differentiation. This suggests a role for loss of this inflammasome in HCC tumor progression, perhaps by allowing the tumor to manipulate its local microenvironment so as to evade attack by the host immune system.

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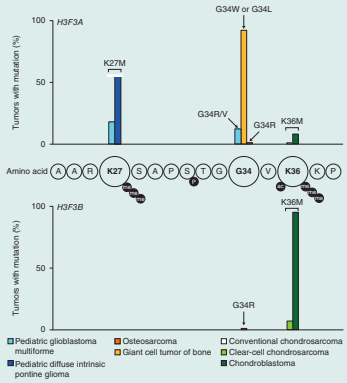
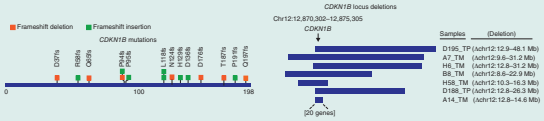
Similar mutations in two bone tumors



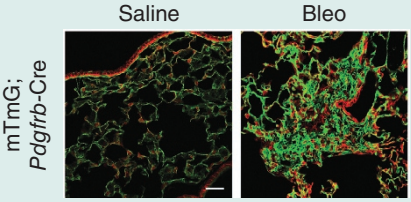
Behjati *et al* identified highly prevalent and recurrent hotspot mutations in histone H3.3 genes (*H3HFA* and *H3HFB*) in chondroblastoma (CB) and giant-cell tumor of bone (GCTB). Slightly different mutations in two very similar genes in two different rare bone tumors suggests variant expressions of a single entity. However, clinically and histologically these two tumors are different. Both are locally aggressive, but CB presents at a young age near the epiphysis whereas GCTB occurs after closure of the growth plate. *IDH* mutations, which are common in chondrosarcoma, are presumed to affect DNA and histone methylation. This study reveals that CB and GCTB show alterations in epigenetic genes. Whereas recurrent chromosomal changes are absent in CB, GCTB features telomeric associations. Clinical inhibition of RANK ligand in GCTB produced by the mononuclear cells prevents recruitment of osteoclasts expressing the receptor, resulting in sclerotic fibrous tissue. The connection between *H3HFB* mutation and RANK ligand expression requires further elucidation.
Nature Genetics 2013;45:1479–1482; doi:10.1038/ng.2814

Cyclin-dependent kinase gene loss-of-function mutations in rare tumors



In a study recently reported in *Nature Genetics*, deletion and insertion frameshifts and locus deletions in *CDKN1B* were observed in ~10 % of small-intestine neuroendocrine tumors. This gene encodes p27, a cyclin-dependent kinase inhibitor gene, which is probably a tumor suppressor in such neoplasms. Amplification of large segments of chromosomes 4, 5, 14, and 20 and deletions of chromosome 18 were common. The pathogenesis of this rare tumor is thus distinct from pancreatic and lung neuroendocrine tumors, in which mutations, both germline and somatic, in *MEN1* are common. In addition, pancreatic neuroendocrine tumors show recurrent mutations in *ATRX*, *DAXX*, *PTEN*, and *TSC2*. Hence, despite some morphologic and immunohistochemical overlap, neuroendocrine tumors in these various organs are distinct. Concordance of mutations in primary and metastatic tumors was high—greater than 99% in measured pairs.
Nature Genetics 2013;45:1483–1486; doi:10.1038/ng.2821

An integrin pathway important for fibrosis



Fibrosis, a critical end point in several organ diseases, is usually recalcitrant to treatments other than organ transplantation. Secretion of transforming growth factor-β is known to be a critical mediator of fibrosis in multiple organs, but its molecular activators are less well understood. Henderson *et al* demonstrated that a *Pdgfrb*-Cre system controlled by the *Pdgfrb* promoter inactivates α_V integrin in myofibroblasts of several mouse organs. Loss of α_V integrin was highly protective against fibrosis induced by bleomycin. This was confirmed using a small-molecule inhibitor of α_V-integrin function. The α_V-integrin subunits combine with sundry β-integrin subunits in myofibroblasts resident in various organs. *In vivo* disruption of these α_V-integrin subunits and certain αβ-integrin dimers can provide broad protection against fibrosis and might have therapeutic efficacy.
Nature Medicine, published online 10 November 2013; doi:10.1038/nm.3282

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