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Modern Pathology

Detecting mutated EGFR protein in lung cancer

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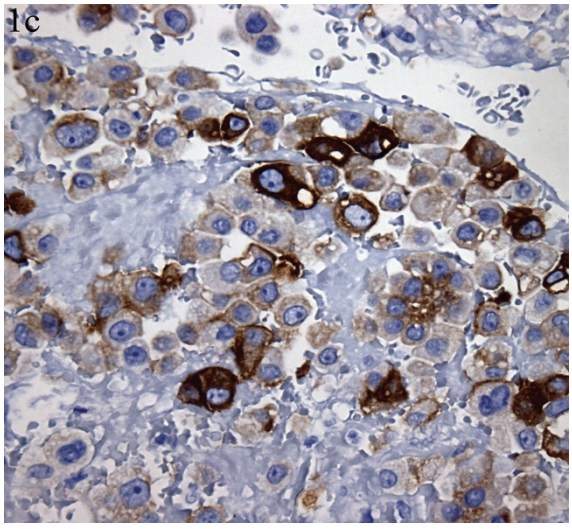

BRAF V600E mutant protein, commonly seen in melanoma, can be detected by antibodies rapidly and with high sensitivity and specificity, although alternative mutations are not recognized. This rapidly defines a population of roughly 30% of melanomas for which additional testing could be avoided. Identification of epidermal growth factor receptor (EGFR) mutations in lung cancer changes clinical management, but these mutations are rare. The ability to efficiently recognize EGFR mutants is important, and immunohistochemistry for mutant protein could accelerate the search. However, because EGFR mutations are rare, a very sensitive method is needed to definitively exclude negative cases from further testing. The two antibodies used by Bondgaard and colleagues in a study evaluating such a method had sensitivities of roughly 60 and 80% for exon 19 and 21 mutant proteins, respectively. The specificities were more laudable, at around 98% each. The negative predictive value of detection with these antibodies is not suited to exclude the majority of cases where EGFR is not mutated.

PTEN and *ERG* in prostate cancer

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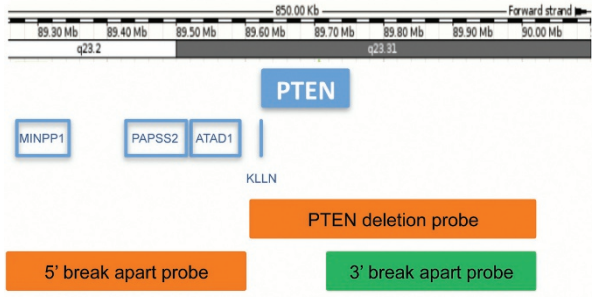
PTEN loss is known to be associated with *TMPRSS2:ERG* rearrangement in prostate cancer and is a biomarker for more aggressive behavior. The sequence of these events is not understood. Using a novel tissue microarray containing cores from 10 tumor blocks from each of 189 prostatectomy specimens, the authors found that *PTEN* loss generally



appeared to arise after *ERG* rearrangement. Having previously been used to examine the tissue microarray for *ERG* status, two fluorescence *in situ* hybridization probe sets for the two major mechanisms of loss of *PTEN* in prostate—deletion and rearrangement—demonstrated significant heterogeneity of *PTEN* aberrations. Although this heterogeneity suggests hurdles to the use of *PTEN* status as a biomarker in needle biopsies, the suggestion that *ERG* rearrangement augments the incidence and/or selection for PTEN loss is of interest and confirms the usefulness of multiply sampling and mapping molecular heterogeneity as a guide to the sequence of molecular pathogenetic events.

Laboratory Investigation

Pericytes of the vasa vasorum are multiplastic

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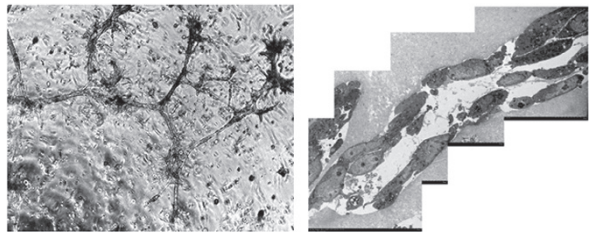

A subset of the pericytes in the adventitial capillaries have been reported to have mesenchymal plasticity, but their role in repair and remodeling in vascular injury is not understood. Using a novel model in which adventitial microvessels from injured vessels of mice with a temperature-sensitive SV40 T-antigen gene could be maintained in collagen-coated tubes, Kabara *et al* derived multiple endothelial and pericyte cell lines. Coincubation of these cell lines recapitulated capillary-like structures in Matrigel. Some of the pericyte cell lines were able to differentiate along mesenchymal and neuronal lineages under appropriate conditions, including adipocytic, osteoblastic, and schwannian routes. While these pericytes may play a

role in tissue repair and remodeling, microvessels from the tunica adventitia can promote neovascularization at areas of atherosclerosis and contribute to plaque evolution. The authors' model allows exploration of the helpful and pathogenic roles of this cellular compartment.

FGF4 fertilizes ovarian stromal soil for cancer seed

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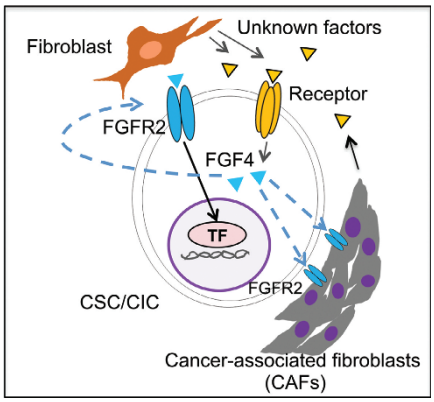

Stromal cells, including cancer-associated fibroblasts, nurture and support cancer cells and facilitate initiation, growth, progression, and metastasis. Yasuda *et al* report that, when cells with properties of cancer-initiating cells isolated from an ovarian carcinoma cell line are mixed and cocultured with cancer-associated fibroblasts, tumor initiation was enhanced in both *in vitro* and *in vivo* assays. Expression of fibroblast growth factor 4 (FGF4) was increased in the cancer cells mixed with cancer-associated fibroblasts, as was that of stemlike markers such as SOX2 and POU5F1. Knockdown of FGFR2, a cognate receptor for FGF2 on the cancer cells, diminished *in vivo* tumor sphere formation. Assessment of a large cohort of ovarian epithelial cancers revealed that increased expression of FGF4 was associated with poor outcome. These results suggest that cancer-associated fibroblasts may help to provide a niche that nurtures cancer cells, with paracrine or autocrine FGF4-FGFR2 signaling supporting this relationship.

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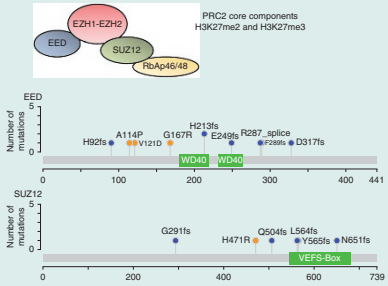
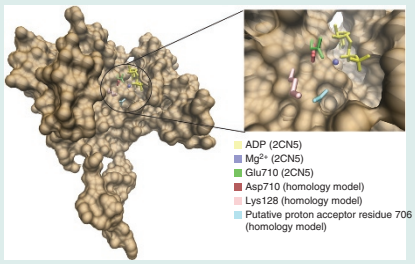
Polycomb repressive complex 2 is critical in MPNSTs



Malignant peripheral nerve sheath tumors (MPNSTs) may arise sporadically in neurofibromatosis type I patients. Biallelic *NF1* inactivation is characteristic of MPNSTs, but it is also seen in neurofibromas and thus not sufficient for malignant transformation. In a study reported in *Nature Genetics*, Lee *et al* demonstrated in MPNSTs a high prevalence of mutually exclusive inactivating mutations in *SUZ12* or *EED*, both elements of the Polycomb repressive complex 2 (PRC2). These mutations showed strong correlation with *NF1* and *CDKN2A* mutations. The *SUZ12* results were also seen in another, independent letter in *Nature Genetics*, by Zhang *et al*. These PRC2 gene mutations are not found in neurofibromas. PRC2 regulates gene expression through histone marks. Specifically, H3K27me3 histone marks are lost along with *SUZ12* and *EED* mutations and restored in cell-line models upon reintroduction of the gene. Nuclear expression of H3K27me3 can be readily assessed by immunohistochemistry and could be further explored as a diagnostic aid in some settings.

Nature Genetics 2014;46:1227–1232; doi:10.1038/ng.3095 and 2014;46:1170–1172; doi:10.1038/ng.3116

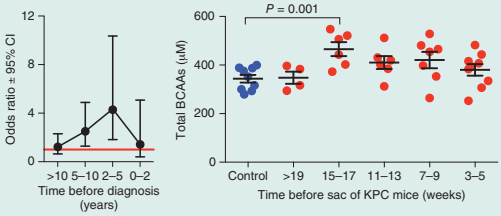
Genomic characterization of salivary PLGAs



Using transcriptomic and exomic approaches, Weinreb *et al* identified two recurrent mutations in more than 70% of salivary polymorphous low-grade adenocarcinomas (PLGAs). Both involved *PRKD1* and resulted in the same amino acid substitution, p.Glu710Asp. These mutations were not found in other salivary tumors, suggesting that they might be disease-defining and thus diagnostically relevant. *PRKD1* encodes a serine–threonine kinase involved in cell adhesion, migration, survival, and vesicular transport. The pattern of focused mutations argues that *PRKD1* is an oncogene; structural modeling based on homologous proteins suggested that these mutations are in the conserved kinase catalytic group. Functional testing showed evidence of increased kinase activation. Because these two equivalent alterations were the only recurrent mutations seen in PLGA, they are likely to represent a newly defined driver-type mutation and novel oncogene in cancer.

Nature Genetics, 2014;46:1166–1169; doi:10.1038/ng.3096

Branched-chain amino acids and pancreatic cancer



Most pancreatic ductal adenocarcinomas are detected at an advanced stage and patients have dismal survival irrespective of treatment modality. Because pancreatic cancer is associated with obesity and glucose intolerance, Mayers *et al*, as reported in *Nature Medicine*, investigated circulating metabolites in prediagnostic plasma from patients and controls in four cohort studies. Elevated plasma levels of branched-chain amino acids were associated with a twofold risk of future pancreatic cancer diagnosis. The strongest association was noted in samples obtained 2–5 years prior to diagnosis when occult disease was probably present. This elevated risk was independent of other known risk factors on multivariate analysis. A *Kras*-driven transgenic mouse model for pancreatic cancer also showed serum branched-chain amino acid elevation, but this was absent in *Kras*-driven tumors at other sites. It appears that pancreatic carcinoma induces a whole-body protein breakdown early in its course.

Nature Medicine, published online 28 September 2014; doi:10.1038/nm.3686

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