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Modern Pathology

Involvement of degradome in squamous cell carcinoma

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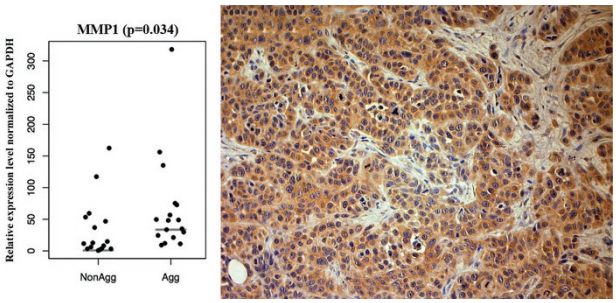

Cutaneous squamous cell carcinoma is usually cured by surgical excision, but it can behave aggressively, and the mechanisms of tumor progression are not well understood. The degradome is composed of proteases that are strictly regulated to modify the local environment, or stroma. There are several protease families, including metalloproteases, disintegrins, and proteases with thromboplastin motifs. These regulated proteases are involved in tissue development and homeostasis, but they are also expressed in a coordinated fashion in cancer to facilitate neoplastic development and tumor invasion. Prasad *et al* used techniques including gene expression arrays, quantitative PCR, immunohistochemistry, and other techniques to examine various protease and other genes and proteins in squamous cell carcinoma in comparison with normal skin. Several proteases were found to be expressed in coordinated fashion in squamous cell carcinoma. In particular, matrix metallopeptidase 1 (encoded by MMP1) was found to be significantly overexpressed in more aggressive tumors.

Uterine smooth muscle tumors with *fumarate hydratase* deficiency

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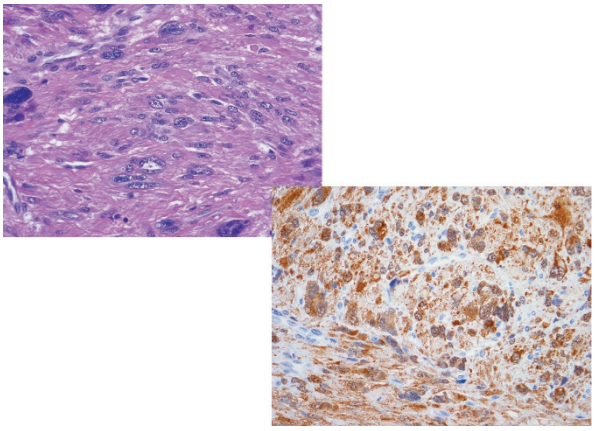
Numerous genetic derangements have been described in smooth muscle tumors. Rarely, *fumarate hydratase* mutations are found in uterine smooth muscle tumors. The loss of fumarate hydratase leads to increased fumarate levels in neoplastic cells, with production of *S*-(2-succino)-cysteine detectable by immunohistochemistry. On the basis of *S*-(2-succino)-cysteine accumulation and testing for germline and somatic fumarate hydratase mutations, Reyes *et al* found that tumors associated with these aberrations showed increased cellularity, staghorn-like vascularity, peculiar fibrillary



cytoplasm with eosinophilic intracytoplasmic globules, inclusion-like nucleoli, and clear perinuclear halos. The study indicates that fumarate hydratase–deficient smooth muscle tumors have characteristic morphologic properties and suggests that this deficiency can be screened for using *S*-(2-succino)-cysteine immunohistochemistry. The findings provide the pathologist with additional tools to identify hereditary leiomyomatosis associated with renal cell carcinoma.

Laboratory Investigation

Superficial tumor scrapings as a source for biobanking and research

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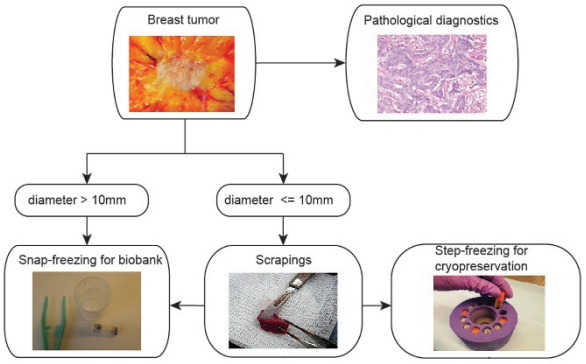

Current treatment guidelines for breast cancer rely on tissue testing for hormone receptors, HER2, and other markers that use immunohistochemistry or fluorescence *in situ* hybridization amenable to formalin-fixed paraffin-embedded (FFPE) tissue. However, newer methods using multiplexed testing of DNA and messenger RNA (mRNA) are increasingly applied. Although these approaches are

being adapted for use with FFPE tissue, fresh-frozen tissue has advantages. Since many breast tumors are less than 1 centimeter in diameter, fresh-frozen material is often unavailable. Ma and colleagues describe a technique in which tissue samples for biobanking and even production of mammospheres is obtained by scraping a scalpel blade across small tumors. These samples are sufficient for standard DNA- and mRNA-based multiplex strategies in which the amount of analyte needed is very small. The authors believe that the technique can extract valuable samples from small tumors for both clinical and research purposes.

Reduced expression of HP1 in thyroid malignancy

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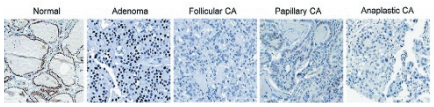

During thyroid tumorigenesis, heterochromatin integrity is compromised. There are three heterochromatin protein 1 (HP1) isoforms—α, β, and γ—that are essential for chromatin packaging. They are differentially expressed in different tissue types and settings and have been shown to be reduced or lost in certain tumor types and with tumor progression. In a comparison of various thyroid tumors with normal thyroid parenchyma, Tretiakova *et al* demonstrated that HP1β was reduced or lost in all but follicular adenomas and that this loss could be at least partially mediated by microRNA dysregulation. HP1α expression was reduced only in metastatic disease and tumors that progressed to a state of poor differentiation. This suggests that reduction of HP1β and HP1α may occur in sequence, perhaps cooperating mechanistically. They do appear to be markers of thyroid malignancy and tumor progression, respectively.

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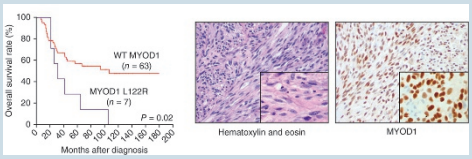
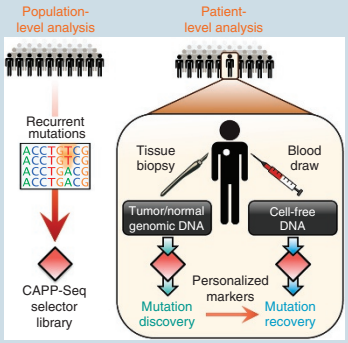
MYOD1 mutations in an aggressive subset of embryonal rhabdomyosarcoma



As reported in *Nature Genetics*, Kohsaka and colleagues used exome and transcriptome sequencing to study embryonal rhabdomyosarcoma and observed that a subset of tumors have an unusual and recurrent mutation in *MYOD1*, which encodes a basic helix–loop–helix (bHLH) transcription factor that promotes myogenic differentiation. There is an invariant leucine encoded by codon 122 in all myogenic bHLH transcription factors including *MYF5*, *MYOG*, and *MRF4*. This same codon encodes an arginine in the *MYC* bHLH family. The recurrent embryonal rhabdomyosarcoma mutation causes a leucine-to-arginine substitution at this site. This blocks the normal functions of MYOD1 and confers binding to MYC consensus regulatory sites, thereby effectively converting a differentiation factor to a proliferative signal. The *MYOD1* mutated cases were hypercellular, and many exhibited spindle-cell morphology. Activating mutations in *PIK3CA* and inactivation of *PTEN* were also noted. Clinically these cases took a more aggressive course.

Nature Genetics 2014;46:595–600; doi:10.1038/ng.2969*

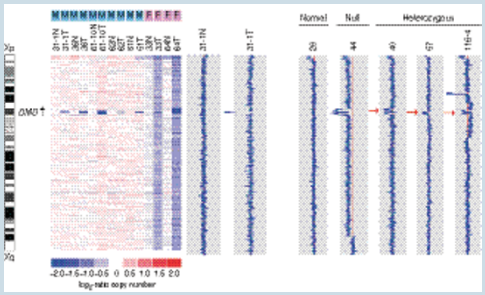
A universal method for quantitating circulating tumor DNA



Circulating tumor DNA (ctDNA) hold great promise for cancer staging. However, applications have been limited by poor sensitivity and inability to robustly differentiate cancer genomes from normal cells. Newman and colleagues explain in *Nature Medicine* how a technique they call cancer personalized profiling by deep sequencing (CAPP-Seq) can overcome these barriers. Using data samples from patients with non–small cell lung cancer, they sequenced genomic portions that contain mutations in more than 95% of tumors. They could detect ctDNA in all patients with stage II–IV disease and half of patients with stage I disease. The specificity was 96% for mutated allele burdens as low as 0.02%. The amount of ctDNA correlated strongly with tumor burden, and the technique allowed more accurate assessment of disease burden compared with standard radiologic approaches. This methodology, which is applicable to most cancer types, could be valuable for clinical tumor monitoring.

Nature Medicine, published online 6 April 2014; doi:10.1038/nm.3519

Dystrophin acts as a tumor suppressor in myogenic malignancies



A significant subset of sarcomas show evidence of myogenic programs—in particular, leiomyosarcoma, rhabdomyosarcoma, and gastrointestinal stromal tumor. *DMD*, encoding dystrophin, is the longest gene in humans and has frequently been found to carry nonfunctional passenger-type mutations in genomic analysis. Dystrophin is a structural protein that links the actin cytoskeleton to the extracellular matrix. However, in a study published in *Nature Genetics*, Fletcher and colleagues found intragenic deletions of *DMD* present in most of the three myogenic sarcoma types listed above, but not in nonmyogenic sarcomas. Dystrophin is expressed in the cognate normal tissues for these tumors, and expression of dystrophin was found to inhibit myogenic sarcoma cell migration, invasion, anchorage independence, and invadopodia formation. Thus, dystrophin appears to be a tumor suppressor specific to sarcomas showing myogenic differentiation.

Nature Genetics 2014;46:601–606; doi:10.1038/ng.2974*

*These two articles featured in this section have USCAP members as authors.