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Modern Pathology

An increasingly important area needing improved accuracy

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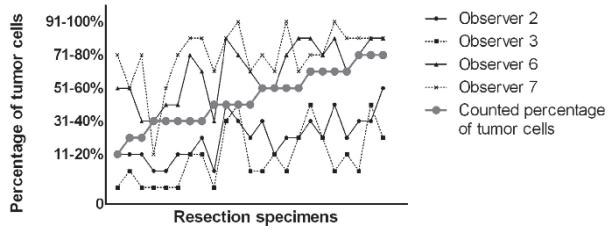
The proportion of cases in which molecular testing is needed to inform clinical management is rapidly increasing. The quality of formalin-fixed paraffin-embedded material available for use in such assays can vary widely. One important consideration, as explained by Smits *et al* in this issue, is the sample's tumor cellular content (or, more accurately, the percentage of tumor nuclei), which is usually estimated from H&E sections. A reliable estimate is key to ensuring that the tumor falls within the known sensitivity or lowest limit of detection of the assay. Correlation with more quantitative sequencing methods, such as next-generation sequencing, in which the precise percentage of mutated and nonmutated amplicons is known, is increasingly important. The investigators found that estimates by experienced pathologists varied widely, both between observers and as compared with manual nuclei counting. The common overestimation of cellularity could lead to false-negative results. The authors suggest that additional training could increase accuracy.



Specific mutations in metastatic uveal melanoma correlate with clinical outcome

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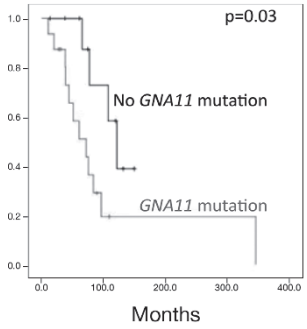
Uveal melanoma, although an uncommon type of melanoma, is the most common malignancy of the eye in adults. Although these tumors lack mutations in *BRAF* or *NRAS*, recent studies have reported activating mutations in the G-protein alpha subunits *GNAQ* and *GNA11* and inactivating mutations in the tumor suppressor *BAP1*. Mutations in *SF3B1* are known to be less common, mutually exclusive with BAP1 loss, and associated with a better outcome. In a study of 30 metastatic melanomas, Griewank *et al* found that most (81%) showed loss of *BAP1*, which is known to be associated with poor outcome. Interestingly, mutations in *GNA11* were common and associated with worse disease-specific survival than



mutations in *GNAQ* or in cases lacking mutations in both genes. Mutations in *SF3B1* were rare in this metastatic population. Although *GNAQ* and *GNA11* are in the same gene family and have precisely analogous mutations, their consequences vary within uveal melanoma.

F. Stephen Vogel Award winner

Congratulations to Ghassan Allo, University of Toronto, Ontario, Canada, as the winner of the 2014 F. Stephen Vogel Award for the best paper by a resident or fellow in an Academy journal. His contribution is entitled "ARID1A Loss Correlates With Mismatch Repair Deficiency and Intact p53 Expression in High-Grade Endometrial Carcinomas." He will receive this prestigious award at the USCAP Annual meeting in San Diego in March.

Laboratory Investigation

Tissue culture models for benign and malignant prostate

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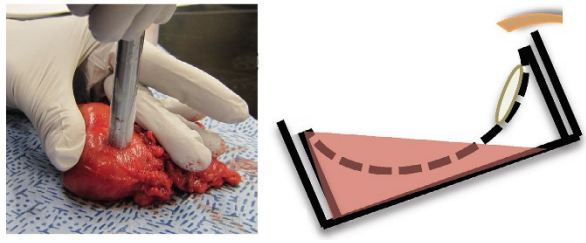

Cell culture is a common method used to study both cancer and normal cells, but such uniform populations of cells lack the richly diverse environment of stroma necessary to recapitulate the complex conditions and functional structure of organs. Maund *et al* present a novel culture method whereby cores are taken directly from the prostate (benign or malignant areas) and grown in media in which they are intermittently submerged to allow uniform

diffusion of nutrients and oxygen. The authors found that the structure and function of the tissue could be maintained for up to five days under ideal conditions. The system was used to examine the effects of piperlongumine, which has previously been reported to specifically reduce androgen signaling in prostate carcinoma. These effects were faithfully recapitulated.

Hepatic stellate cells promote tumor progression through immunomodulatory effects

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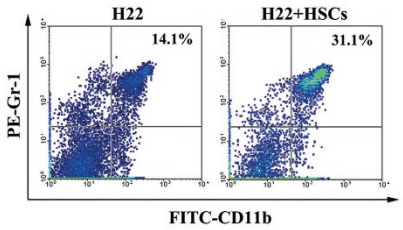

The tumor microenvironment is increasingly recognized as a critical mediator of tumor progression. Within the microenvironment of the liver, hepatic stellate cells (HSCs) are known to exert strong immunomodulatory effects. Zhao *et al* had previously demonstrated that HSCs can help create a permissive immunosuppressive environment for the growth of hepatocellular carcinoma (HCC). Extending these intriguing findings, the same group now demonstrates that activated HSCs induce local angiogenesis and lymphangiogenesis, and also promote more systemic immunosuppression by expanding the populations of regulatory T cells and myeloid-derived suppressor cells in the local tumor bed as well as in the spleen and bone marrow of a mouse model. This suggests a critical immunomodulatory role for these cells in HCC tumor progression. HCC may use HSCs and subvert their role in creating hepatic immunotolerance, which normally allows proper organ function, and instead exploit this function to avoid host immune detection.

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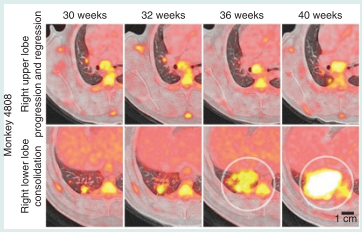
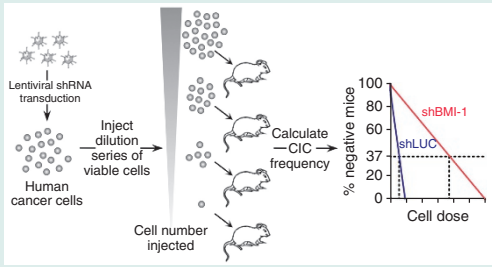
Sterile granulomas are common in tuberculosis



Pathologists are well aware of the difficulty in identifying *Mycobacterium tuberculosis* in granulomas. Special stains and long searches under high power and oil immersion can be required. In a recent paper in *Nature Medicine,* Lin and colleagues provide some insight into the problem. Although more than 30% of the world's population is infected with tuberculosis, only 5–10% will express disease. The causes of this latency are not understood. Using a macaque model, the authors demonstrated that most lung lesions are founded by a single bacterium and grow to similar extents. Local factors, such as the onset of adaptive immunity, dictate the fate of individual infective sites. Some granulomas will be sterile and others will have viable organisms, even within the same animal. Although local factors regulating the fate of infection sites need to be better understood, sterile granulomas appear to be a feature of tuberculosis.

Nature Medicine, published online 15 December 2013; doi:10.1038/nm.3412

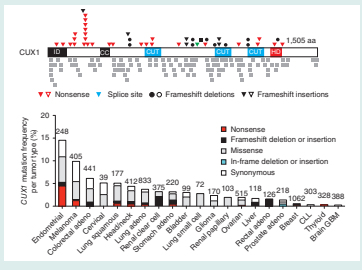
Targeting self-renewal in colorectal carcinoma



In a study reported in *Nature Medicine,* Kreso and colleagues tested the theory that cancer-initiating cells (CICs) mediate cancer survival and recurrence after therapy. CICs are believed to show an enhanced capacity for self-renewal, resistance to chemotherapy, and avoidance of apoptosis, as well as an ability to lie dormant. These properties suggest a role for them in tumor recurrence. The authors found that the self-renewal regulatory protein BMI-1 is required for colorectal tumor formation and specifically for CIC function. When BMI-1 was stably knocked down in multiple cell lines, growth was inhibited in culture and in xenograft models. In addition, fewer tumors were generated. Additional experiments demonstrated that the ability for self-renewal was inhibited; this appeared to be mediated by the CICs. Treatment with PTC-209, a BMI-1 inhibitor, showed similar effects. These results indicate that CICs can be targeted and that doing so is effective in reducing tumor growth and progression. Specific inhibition or destruction of the CIC population thus appears to be a viable strategy for cancer therapy, at least in this model system.

Nature Medicine, published online 1 December 2013; doi:10.1038/nm.3418

Low-frequency inactivating *CUX1* mutations promote tumorigenesis



Low-frequency somatic mutations that drive tumorigenesis can be difficult to detect in genomic studies. Wong *et al* scanned the genomic data for 7,651 cancers from 28 different tumor types for genes with a significantly elevated ratio of observed to expected non-sense mutations, which strongly suggests an encoded tumor suppressor. The authors noted several known tumor suppressor genes as well as new genes, including *CUX1*. Because *CUX1* was found to be inactivated in less than 15% of tumors of many types, it appears to be a generalized but infrequent event. The investigators demonstrated that *CUX1* mutations are associated with inferior survival in myeloid malignancies. Using mouse and Drosophila models, they found that *CUX1* deficiency allows increased PI3K activity mediated by loss of expression of the PI3K inhibitor gene, *PIK3IP1*, which is directly and positively regulated by *CUX1*. Hence, although *CUX1* inactivation may be uncommon in cancer, it leads to upregulation of PI3K, one of the most important pathways in cancer and the target of an increasing number of anticancer drugs.

Nature Genetics 2013;468:33–38; doi:10.1038/ng.2846