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Modern Pathology

Stromal signatures in endometrioid endometrial carcinomas

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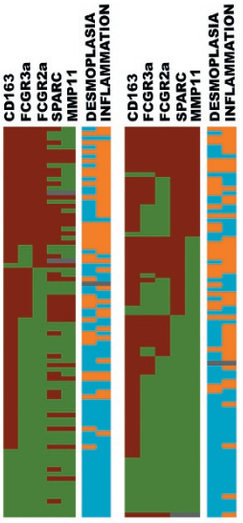

Stromal signatures in endometrioid endometrial carcinomas are correlated with histologic features of the tumor. Two stromal signatures—one rich in macrophages (colony-stimulating factor 1 (CSF1)-driven), the other similar to desmoid fibromatosis/desmoplasia—have been described in breast cancer as as correlating with outcome. In a study of endometrioid endometrial carcinomas, Espinosa *et al* definitively identified these signatures in 27% and 15%,respectively. Another 13% showed evidence of both, and more than half lacked either signature, in contrast to the previous observations by this same group in breast carcinoma. The CSF1-driven signature, which was retained in metastases, was, not surprisingly, associated with mononuclear cell infiltrates as well as with higher-grade, lymphovascular invasion and oncogenic *PIK3CA* mutations. These studies suggest that targeting the CSF1 pathway should be explored as a therapeutic option.

TERT promoter mutations are common in certain cutaneous tumors

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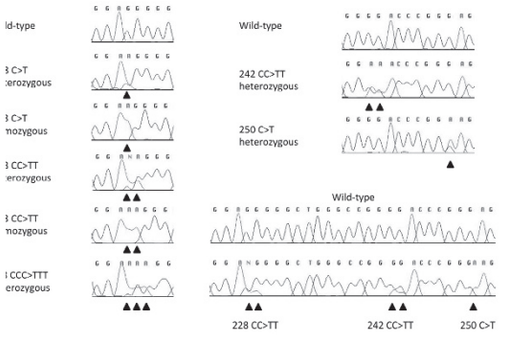
TERT promoter mutations were first recognized as potential somatic oncogenic events in melanoma that lead to increased telomerase expression and improved cellular survival. In this issue, two groups show the same mutations in a significant proportion of other tumor types: Griewank *et al* in atypical fibroxanthomas (93%) and pleomorphic dermal sarcomas (76%) and Scott *et al* in basal cell carcinomas (78%) and squamous cell carcinomas (50%). As with melanoma, these mutations show a characteristic C>T or CC>TT base pair change suggestive of damage induced by solar radiation consistent with known epidemiologic factors in these cutaneous tumors. The *TERT* promoter mutations were not seen in benign neoplasms used as controls. Although more tumors representing a wider spectrum remain to be



investigated, these results suggest that *TERT* promoter alterations, which are presumably oncogenic, may be the most common oncogenic mutations in cutaneous malignant neoplasms.

Laboratory Investigation

An index for assessing tissue quality

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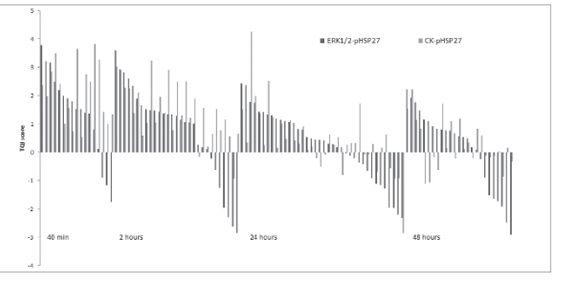

Preanalytic variables such as time to fixation are known to affect epitope recognition by immunohistochemistry; however, there are few objective tests for evaluating tissue quality. Neumeister and colleagues addressed this problem by stabilizing expression levels for cytokeratin, ERK1/2, and phosphorylated HSP-27 on a training set of breast tumor samples with known, increasing cold fixation times using quantitative immunofluorescence. The expression profile of these three epitopes was used to develop a tissue-quality index (TQI) that significantly correlated with known cold ischemic time in two validation cohorts. Negative TQI values were associated with increased cold ischemic time and loss of estrogen receptor staining, suggesting an ability to predict inferior tissue quality in a reasonably objective fashion. The TQI could be useful in assessing samples of dubious provenance for quality and retention of clinically relevant epitopes.

Fucoidan protects against diabetic vascular complications

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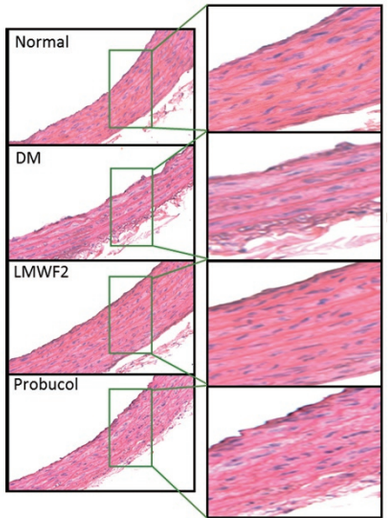

Endothelial dysfunction caused by reduced activity of nitric oxide synthase (eNOS) has been implicated in the development of both micro- and macrovascular complications of type 2 diabetes. Enzymatic activity of eNOS is regulated via phosphorylation of specific sites on the protein; phosphorylation at Ser1177, in particular, improves nitric oxide (NO) bioavailability. Cui *et al* found that in a rat model of type 2 diabetes, administration of low-molecular-weight fucoidan (LMWF), a sulfated polysaccharide obtained from algae, promoted vasodilation and prevented arterial damage. LMWF increased expression of both eNOS and NO release in diabetic rats and endothelial cell cultures; the increase was associated with enhanced phosphorylation at the eNOS Ser1777 site. The endothelial protection provided by fucoidan, its antiproliferative and anti-inflammatory activity as demonstrated in other studies, and its good safety profile justify further studies of the drug's utility in prevention and treatment of cardiovascular complications so prevalent in diabetics.

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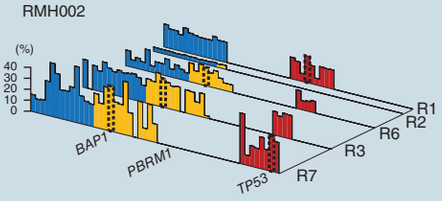
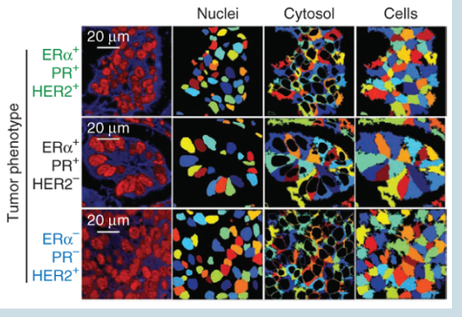
Intratumoral heterogeneity of genomic drivers in renal cell carcinoma



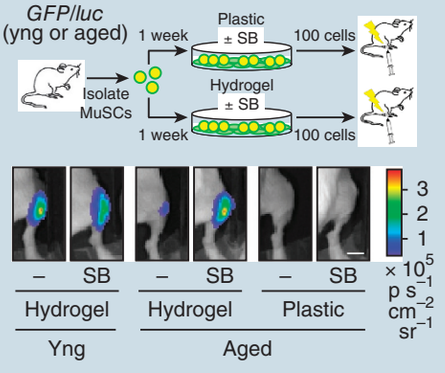
In a recent report in *Nature Genetics*, Gerlinger *et al* describe the intratumoral diversity of genomic cancer drivers in clear-cell renal cell carcinoma. The degree of spatial heterogeneity is daunting. Fully 75% of driver events are subclonal, with *VHL* mutation or methylation and loss of 3p the only events uniformly present in every cell of every case tested—so-called trunk events. Most mutations are seen in isolated subpopulations or branches. The authors' analysis suggests that the degree of intratumoral heterogeneity is underestimated when 5 to 10 independent spatial samples are used and that additional subclones would be found if more samples were obtained. The genetic diversity is similar to the divergent evolution of groups from a common ancestor when populations become geographically isolated. Analyzing a single biopsy for driver mutations in order to choose an appropriate systemic therapy may be inadequate for documenting the driver events present as subclones within a tumor.
Nature Genetics 2014;46:225–233; doi:10.1038/ng.2891

Hectaplex immunohistochemistry for tissue sections



Analysis of multiplexed immunohistochemistry is limited by overlapping and convoluted signal spectra detected in the labeling probes. Angelo and colleagues used secondary ion mass spectrometry to image antibodies linked to pure-isotope elemental metals. Multiplexed ion beam imaging could then be used to detect as many as 100 targets simultaneously, with robust readings over a five-log dynamic range on standard formalin-fixed, paraffin-embedded sections. This technique could have many applications in research and drug discovery in which more comprehensive detection and analysis of expression profiles of numerous analytes would contribute greatly to our understanding of the effects of experimental manipulation of cells. From a clinical perspective, this might allow heavily multiplexed detection of signals, equivalent to the type of coexpression analysis performed with flow cytometry on a fixed tissue section.
Nature Medicine 2014; published online 2 March 2014; doi:10.1038/nm.3488

Rejuvenating stem cells in muscles restores strength lost through aging and injury



Muscle atrophy is common with age. Cosgrove *et al* report their finding that impairment of muscle regeneration in mice with age is due in part to functional deficits in muscle stem cells. The stem cells of aged mice have a reduced capacity to repair myofibers and repopulate the stem cell niche *in vivo* after transplantation. The stem cells from aged mice exhibit senescence markers and are not rejuvenated by transplantation into the muscle microenvironment of young mice. However, the aged stem cells can be rejuvenated by inhibiting p38α and p38β of the extracellular regulated kinase pathways combined with soft hydrogel culturing. Subsequently, they regain the ability to strengthen damaged muscles in aged mice and can be serially transplanted. This work could lead to development of autologous muscle stem cell transplantation to reverse the effects of muscle aging.
Nature Medicine 2014;20:255–264; doi:10.1038/nm.3464