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MODERN PATHOLOGY

Microsatellite shift in MSI high endometrial cancer

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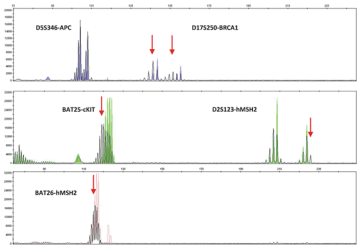

Clinical assessment of mismatch-repair deficiency is a key diagnostic feature in identification and triage of patients with high-stage or recurrent solid malignancies prior to immunotherapy. Microsatellite shift patterns of high microsatellite instability (MSI-H) endometrial and colorectal cancer samples studied by Wu et al. showed minimal microsatellite shift in 52% of MSI-H endometrial cancers. Of the MSI-H endometrial cancers with minimal microsatellite shift, 65% showed combined *MLH1* and *PMS2* loss, 8% had combined *MSH2* and *MSH6* loss, and others showed individual loss of either *MSH6* or *PMS2*. While *MSH6* loss frequently leads to minimal microsatellite instability, this study revealed a higher frequency of *MSH6* loss in MSI-H endometrial cancers. This potentially can lead to misinterpretation of a tumor as either having low microsatellite instability or being microsatellite-stable. The authors conclude that the minimal microsatellite shift in endometrial carcinoma is crucial for determining MS status and guiding therapeutic decisions with regard to checkpoint-inhibitor immunotherapy.

Automating IHC evaluation for stratifying T1 colorectal cancer

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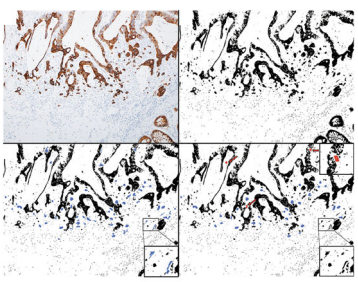

Imaging techniques that require operator interpretation for quantification can fall prey to interobserver variability. The selection of budding foci in stratifying T1 colorectal cancer is one such susceptible imaging technique. Using retrospective samples of 463 T1 colorectal cancer cases, Takamatsu et al. developed a computer-assisted semiautomatic quantification method to reduce this variability by determining the optimal cutoff value to predict the risk of lymph node metastasis. After tumor budding foci had been counted manually, Image J software was employed on cytokeratin immunohistochemistry–stained samples. Both methods revealed several distinct features of and predictive factors for lymph node metastasis. The predictive and observed lymph node metastasis frequencies were confirmed to be highly correlated in the validation dataset. This semiautomated method yielded closer interobserver agreement and enabled more clinically significant predictions and improved therapeutic decision making.

LABORATORY INVESTIGATION

Discovering biomarkers from bone

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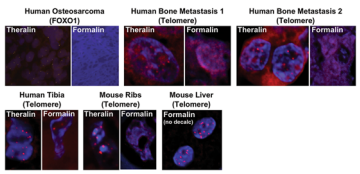

Mueller et al. developed a fixation method to make bone tissue accessible via immunohistochemistry and fluorescence in situ hybridization (FISH) by simultaneously fixing and decalcifying the tissue. Using 50 patient-matched primary bone cancers, the group compared formalin fixation and decalcification with theralin fixation with and without decalcification. The results with theralin fixation were comparable to those with formalin-fixed, decalcified samples, but with improved tissue histomorphology. Protein and DNA extraction by laser-capture microdissection and reverse phase protein microarrays was more productive in the theralin-fixed samples. Theralin-fixed samples also did not have the artifact observed in formalin-fixed samples, in which quantification of β-actin directly correlated with fixation time. The group proposes that their method allows

assessment of drug efficacy in bone tissue studies and facilitates identification of bone-related biomarkers. This opens new avenues of investigation for primary bone cancers as well as cancers that metastasize primarily to bone.

Quantifying HER2 with spatial association

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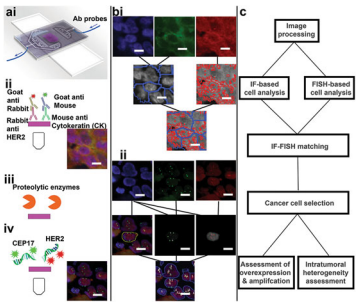

Tumors are rarely completely uniclonal, and Nguyen et al. sought to develop an assay that could account for this intratumoral heterogeneity and quantify expression patterns of HER2. Using microfluidic technology and image processing, they were able to characterize HER2 protein overexpression and *HER2* gene amplification by performing sequential steps on the same slide. Their protocol consisted of (1) immunofluorescence using a microfluidic protocol, (2) elution to remove the immunofluorescence staining agents, (3) fluorescence in situ hybridization (FISH), and (4) automated quantitative cell-by-cell image processing to analyze the local indication of spatial association (LISA). The group developed an algorithm for analyzing spatial association to distinguish cluster and mosaic intratumoral heterogeneity from artifacts by using thin tissue sections. With bigger sample sizes, the technique could be validated to further explore possible links between intratumoral heterogeneity and cancer prognosis.

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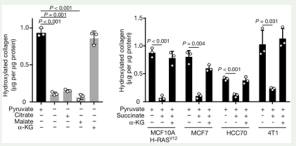
Pyruvate collagen remodeling in metastasis

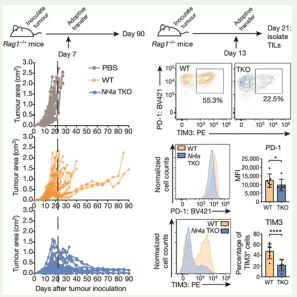
In order to metastasize, cancer cells can adjust the extracellular matrix that dictates their local environmental niche by hydroxylating collagen. Elia et al. used in vitro spheroids and in vivo xenograft models to demonstrate a pathway of extracellular matrix adjustment by breast cancer cells in the lung metastatic niche. Breast cancer cells rely on pyruvate uptake on multiple levels: to induce production of α-ketoglutarate, to increase the activity of collagen prolyl-4-hydroxylase, and to drive collagen remodeling in lung metastases. Metabolic assays demonstrated that alanine aminotransferase was crucial in the pyruvate-driven production of α-ketoglutarate. Inhibition of pyruvate significantly reduced the generation of lung metastases in mouse models of breast cancer. This suggests that pyruvate-driven collagen remodeling should be a priority for further investigation and that its manipulation might result in therapeutic benefit.



Nature, published online 27 February 2019; https://doi.org/10.1038/s41586-019-0977-x

Nr4a as target for immunotherapeutics

T cells expressing chimeric antigen receptors (CAR T cells) targeting human CD19 (hCD19) have been clinically effective against B-cell malignancies, but CAR T cells have shown limited efficacy against solid tumors. Chen et al. transferred hCD19-reactive CAR T cells into hCD19^{+} tumor-bearing mice in order to assess downstream effects. They found that CD8^{+} T cells from patients with cancer or chronic viral infections expressed high levels of NR4A transcription factors. *Nr4a* triple-knockout CAR T cells (i.e., lacking all three gene family members) promoted tumor regression and prolonged survival of tumor-bearing mice. Assessing chromatin structure in the *Nr4a* triple-knockout cells also identified binding motifs for NF-κB and AP-1, transcription factors that are involved in the activation of T cells. Since PD-1 blockade caused a significant decrease in *Nr4a* mRNA, these transcription factors are being proposed as an important target for cancer immunotherapy owing to their role in cell-intrinsic T-cell hyporesponsiveness.



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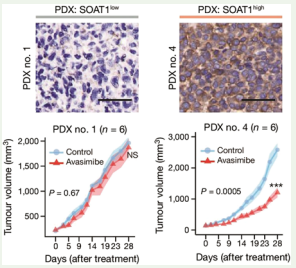
Identifying therapy targets in hepatocellular carcinoma with proteomics

Jiang et al. applied performed proteomic and phospho-proteomic profiling to a sample size of 110 paired tumor and nontumor tissues of clinically early-stage hepatocellular carcinoma related to hepatitis B infection. Heterogeneity in the samples allowed the researchers to group the cases into three subtypes—S-I, S-II, and S-III—based on clinical outcome. S-III demonstrated disrupted cholesterol homeostasis, the lowest overall survival rate, and the worst prognosis after first-line surgery. When distinct pathways, including glycolysis, cholesterol metabolism, and immunosuppression, were explored, S-III also demonstrated elevated expression of sterol O-acetyltransferase (SOAT1). Targeted knockdown of SOAT1 altered the distribution of cellular cholesterol and suppressed proliferation and migration of cells. In vivo xenograft models demonstrated notable reduction of tumor sizes upon treatment with avasimibe, an inhibitor of SAOT1, when SOAT1 expression in tumors was elevated. This new stratification system indicates the importance of disrupted cholesterol homeostasis for tumor progression and suggests targeting of this pathway.



Nature 2019;567:257–261; https://doi.org/10.1038/s41586-019-0987-8