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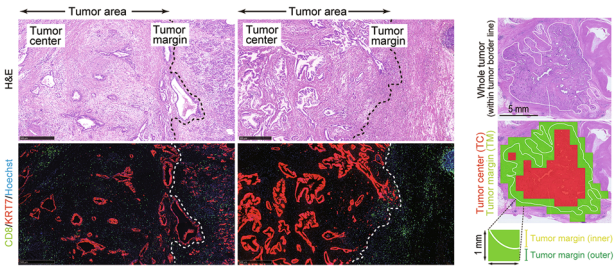
https://doi.org/10.1038/s41379-019-0361-2

MODERN PATHOLOGY

Immune microenvironment of pancreatic adenocarcinoma

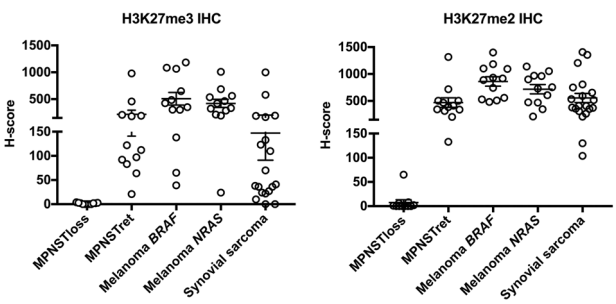
https://doi.org/10.1038/s41379-019-0291-z



$CD8^+$ T cells infiltrate the tumor microenvironment, but the relationship between the levels of infiltration and prognosis is insufficient to influence therapeutic efficacy. Masugi et al. characterized the levels and distribution of $CD8^+$ T cells using multiplex immunohistochemistry-based image analysis in 214 pancreatic ductal adenocarcinoma samples, focusing on the tumor center, the tumor margin, and the whole tumor. They correlated these measurements with cancer-specific survival, adjusting for other clinicopathologic and immune-related features. While there was substantial heterogeneity in their data, they identified features and demonstrate patterns that showed significance. The association of higher $CD8^+$ cell density with prolonged survival was significant for the whole tumor, stronger for the tumor center, and not significant for the tumor margin. Thus, there seems to be validity to assessing the tumor immune microenvironment, but the type of measurement is important.

A more specific biomarker for MPNST

https://doi.org/10.1038/s41379-019-0287-8

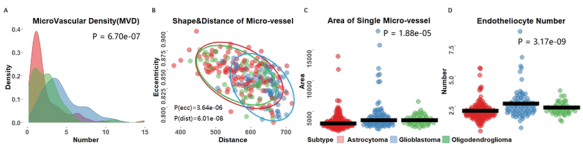


Marchione et al. confirmed that a subset of malignant peripheral nerve sheath tumors (MPNSTs) have loss of histone H3K27 trimethylation (H3K27me3) due to driver mutations affecting the polycomb repressive complex 2 (PRC2). However, this is not an ideal diagnostic biomarker as this loss has been shown in other cancer types in a PRC2-independent fashion. Seeking to find a more specific marker for PRC2 loss, the group explored the mechanism underlying this loss. They found that loss of dimethylation of H3K27 could be this marker; demonstrating loss of H3K27me3 across multiple cell types, with loss of H3K27me2 more specifically lost in MPNST with similar sensitivity to H3K27me3 loss. PRC2 loss occurs in other tumor types and therefore H3K27me2 loss is not a completely specific marker for peripheral nerve sheath tumors; however, the authors note that it is considerably more specific than H3K27me3, suggesting efficacy in the clinical setting.

LABORATORY INVESTIGATION

Deep learning for microvascularity in glioma

https://doi.org/10.1038/s41374-019-0272-3

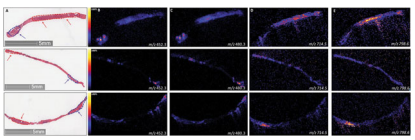


An automated technique for accurately quantifying the microvascularity of gliomas could play a critical role in the early staging of these tumors since vascularity is correlated with grading and subtype. Li et al. developed deep-learning algorithms designed to detect and quantify microvascularity in 350 hematoxylin and eosin–stained samples from glioma patients. Assessed microvascular features were correlated with histologic types, molecular types, and patient prognosis. The algorithm was able to distinguish between molecular types of glioma (glioblastoma vs. TERT-mutated), as well as cluster groups based on

different survival periods, indicating a role in determining prognosis. The group proposes that their algorithm could have a crucial role in early diagnosis and determination of prognosis of patients with various glioma types in real time in the clinic.

DESI-MSI: new prognostic tool for prostate cancer

https://doi.org/10.1038/s41374-019-0265-2

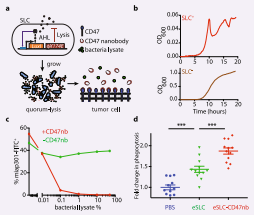


Morse et al. sought to explore and validate the use of desorption electrospray ionization coupled to mass spectrometry imaging (DESI-MSI) as a potential adjunct to diagnostic surgical pathology in clinical studies of prostate cancer. The authors used 900 spatially resolved DESI-MSI spectra to establish an accurate, high-resolution metabolic profile of prostate cancer. They identified two lysophosphatidyletholamines with abundance that decreased with cancer grade and two phosphatidylcholines with increased abundance with increasing cancer grade. Using 534 spatial regions of interest in the training cohort and 430 regions of interest in the test cohort, they developed a multivariate metabolomic classifier for prostate cancer that achieved 97% balanced accuracy. They conclude that this technique could be used to characterize prostate cancer metabolism during early surgical diagnostic procedures, alongside traditional pathology characterization.

nature.com/pathology

Truly targeted delivery of immunotherapeutics

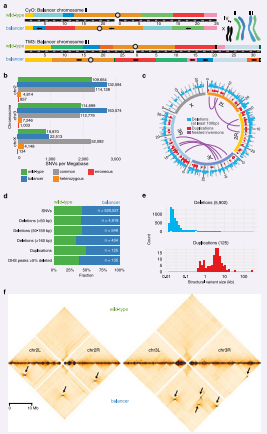
Chowdhury et al. explored the creation of engineered therapeutic systems that intelligently sense and respond to diverse environments, ultimately adding specificity and efficacy to previous systemic therapeutics. The group engineered a strain of *Escherichia coli* to specifically lyse within the tumor microenvironment and release an encoded nanobody antagonist of CD47 (CD47nb). The release induced rapid tumor regression, prevented metastasis, and led to long-term survival in a syngeneic tumor model in mice. This induction of immune responses was greater than those observed after treatment with an anti-CD47 monoclonal antibody alone. The group further demonstrated antitumor effects in untreated lesions, indicating an abscopal-type effect of their payload delivery from the engineered bacteria. The authors propose that their methods allow spatiotemporally defined delivery of immunotherapeutics with abscopal effects for treating metastatic disease by simply injecting the most accessible lesions.



Nature Medicine 2019;25:1057–1063; https://doi.org/10.1038/s41591-019-0498-z

Chromatin structure and function unzipped

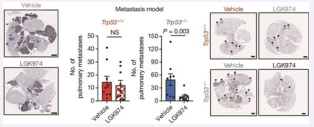
The complex three-dimensional spatial architecture of the genome shows prominent topological features such as blocks of heterochromatin and euchromatin, chromatin domains, and chromatin loops. It has long been thought that these features were intricately linked to function. Chromatin loops were thought to bring enhancers into the proximity of their target promoters at topologically associating domains. Ghavi-Helm et al. developed a strategy using *Drosophila* to experimentally distinguish between and manipulate chromatin structure and showed that only 10% of genes tested were affected by large-scale disruption of their natural chromatin position. Other genes were affected by changing their position relative to chromatin structure, but changes in chromatin topology were not neither predictive of changes in nor a major driver of gene expression. These results are in line with the view that function drives structure in the genome at least as much as structure drives function.



Nature Genetics 2019;51:1272–1282; https://doi.org/10.1038/s41588-019-0462-3

p53 as a driver of inflammation in breast cancer

A causal relationship has been illustrated between neutrophils and metastasis in some cancers, and Wellenstein et al. sought to discover the cancer cell-intrinsic mechanisms that govern heterogeneity in neutrophil infiltration. Cancer cell-intrinsic p53 was shown to be a key regulator of prometastatic neutrophils in a panel of 16 mouse models for breast cancer. Loss of p53 in cancer cells induced the secretion of WNT ligands that stimulate tumor-associated macrophages to produce IL-1β, thus driving systemic inflammation. The group then assessed pharmacological and genetic blockade of WNT signaling in p53-null cells, leading to a reduction in metastatic formations. The authors therefore conclude not only that the status of p53 is a prognostic factor in determining metastatic potential but also that WNT signaling could be a promising therapeutic target for patients with p53-deficient breast cancers.



Nature 2019;572:538–542; https://doi.org/10.1038/s41586-019-1450-6

Emma Judson contributed to these reviews.