Modern Pathology (2020) 33, 1636–1637

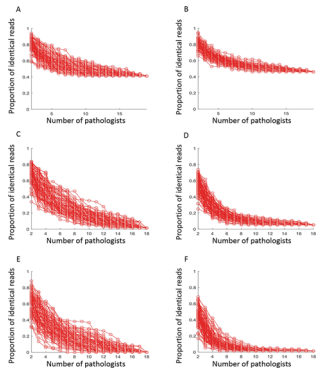
INSIDE THE USCAP JOURNALS

https://doi.org/10.1038/s41379-020-00652-2

MODERN PATHOLOGY

Differential testing of two approved PDL1 assays

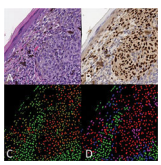
https://doi.org/10.1038/s41379-020-0544-x



Identifying a biomarker as a potential diagnostic tool is only the beginning; the next step is the evaluation and validation of its usefulness in testing. Reisenbichler et al. compared SP142 and SP263 assays and interpreted the percentage and immune cell (IC) staining by 19 pathologists across 14 academic institutions, utilizing a method they call ONEST ("observers needed to evaluate subjective tests") to ascertain the minimum number of evaluators needed to estimate concordance. By identifying IC and concordance between cases, the SP142 assay was determined to be inferior to the SP263 assay in interpreting PDL1 positivity. Using ONEST plots, the authors found that more observers were needed to reach agreement using SP263 compared with SP142, and that IC detection was often difficult to reproduce—the analysis suggested that more than half of pathologists will disagree about IC scores. The US Food and Drug Administration has approved SP142 for determining eligibility for atezolizumab therapy, but these data indicate that patients might be receiving the treatment who are not likely to benefit, whereas others who might benefit are not receiving the treatment.

Virtual IHC could save tissue, time, and money in cancer diagnostics

https://doi.org/10.1038/s41379-020-0526-z

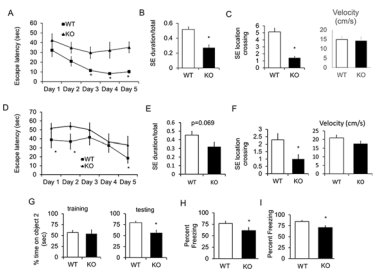


Immunohistochemistry (IHC) is a widely used diagnostic technique, but it can be costly and demanding because of the amount of tissue needed. Jackson et al. proposed a machine-learning algorithm that would enable the use of simple hematoxylin and eosin (H&E) staining to provide the same data. The group performed H&E staining on 12 slides and registered images before destaining, and then performed IHC for SOX10 and registered a second set of images. The two images for each sample were compared, and color-thresholding and machine learning techniques were employed to identify 3,396,668 SOX10-negative cells and 306,166 SOX10-positive cells, which became the basis for a convolutional neural network trained to predict SOX10 nuclear staining. The resulting virtual IHC neural network achieved an area under the curve of 0.9422 in an analysis of receiver operator characteristics when sorting individual nuclei. The authors note that more work is needed but that this technology could have a wide-ranging impact on the diagnosis and treatment of cancer patients.

LABORATORY INVESTIGATION

Nervous system–specific NRBF2 KO results in memory and learning deficits

https://doi.org/10.1038/s41374-020-0433-4

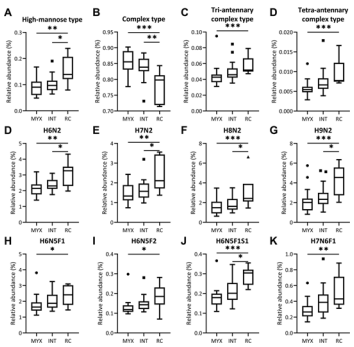


Ouyang et al. explored the role of nuclear receptor binding factor-2 (NRBF2) in learning and memory. The group hypothesized that NRBF2 deficiency plays a role in cognitive deficits. They developed a mouse model with a specific nervous system knockout (KO) of NRBF2 that resulted in profound learning and memory deficits without impact to motor coordination; the mice were able to spend as much time as wild-type controls on a rotarod but had longer escape latencies. RNAseq analyses showed altered expression of genes that have been shown to impact neuronal function. NRBF2 modulates transcriptional activities of retinoic acid receptor α and retinoid X receptor α, and the autophagic activities of

BECN1-VPS34, all known to be involved in neuronal function. Further investigation may determine whether these changes contribute to learning and memory or are an adaptive response that attenuates deficits. Either way, the results could enhance our understanding of Alzheimer's disease.

N-glycans in tumor progression

https://doi.org/10.1038/s41374-020-0435-2



Heijs et al. examined the prognostic significance of areas of mixoid liposarcoma exhibiting increased cellularity, given that the presence of hypercellular round-cell areas is known to be associated with poorer prognosis. Mixoid, intermediate, and round-cell populations of cells were analyzed using matrix-assisted laser desorption/ionization mass spectrometry imaging to analyze the spatial distribution of *N*-linked glycans. The data revealed that increased relative abundances of high-mannose type glycans were associated with tumor progression. An increase of tri- and tetra-antennary *N*-glycans was observed, with morphological tumor progression and increased tumor histological grade as well as poor disease-specific survival, even as overall levels of complex-type glycans decreased. The authors conclude that the intermediate morphology is a transitional state between myxoid and round cell, but that this is reliant on a shift in *N*-glycan expression, pointing to *N*-glycans as a clear target for further research in tumor development and therapeutics.

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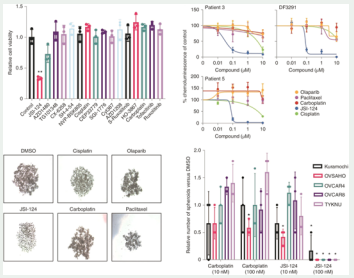
JAK-STAT pathway as a possible therapeutic target in ovarian cancer

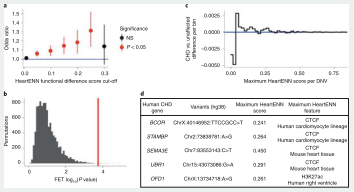
Izar et al. provide a comprehensive characterization of the ascites ecosystem from patients with high-grade serous ovarian cancer (HGSOC) because the development of ascites is a prognostic indicator of drug resistance and poor prognosis. Using single-cell RNA sequencing of 22 ascites specimens from 11 patients, the authors found significant interpatient variability in composition and functional programs of ascites cells. The JAK-STAT pathway may have a role in inflammatory programs of malignant cells within a patient's ascites, and a drug screen using 15 compounds targeting this pathway identified JSI-124 as a potent inhibitor of cell viability. Interactions between cancer-associated fibroblasts (CAFs) and macrophages in the ascites ecosystem regulate or enhance cancer cell–autonomous programs. The putative interaction between CAFs secreting interleukin-6 to stimulate JAK/STAT signaling in cancer cells is associated with poor prognosis and resistance to chemotherapies, making this a promising target for further evaluation in HGSOC.



Nature Medicine, published online 22 June 2020; https://doi.org/10.1038/s41591-020-0926-0

Human CHD associated with cardiac regulating DNVs

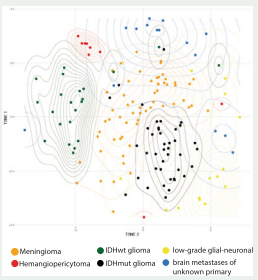
Eight percent of patients with congenital heart disease (CHD) show coding de novo variants (DNVs). Whole-exome sequencing genome comparison of 749 CHD probands, their parents, and 1611 unaffected trios revealed a burden of DNVs in individuals with CHD compared with controls. Significant overlap between transcription-based approaches was observed, and CHD DNVs altered transcription levels in 5 of 31 enhancer assays. Genes associated with DNVs include *JPH2*, which encodes junctophlilin-2, a membrane protein necessary for T-tubule formation, and *SEMA4B*, which is highly expressed in developing heart. Richter et al. also observed a DNV burden in RNA-binding-protein regulatory sites. An enrichment of potentially disruptive regulatory noncoding DNVs could be seen in a proportion of CHD patients at least equal to that observed for damaging coding DNVs. This study, on a larger scale, could further elucidate the magnitude of noncoding effects in CHD genetics, resulting in better opportunities for diagnostics and therapeutic development.



Nature Genetics, published online 29 June 2020; https://doi.org/10.1038/s41588-020-0652-z

Circulating DNA provides ID of intracranial tumors

For any cancer, the ability to diagnose without invasive surgery or biopsy procedures is desirable, but it may be even more crucial in intracranial tumors, for which surgery can pose a particularly high risk. Nassiri et al. propose a noninvasive method for determining primary cell-of-origin lineages of intracranial tumors using plasma DNA-methylation profiles. Their method of cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) discriminated between patients with gliomas, those with a systemic cancer, and healthy individuals on the basis of differentially methylated regions that are hypermethylated in glioma patients. Additionally, this technique was able to distinguish between common intracranial tumors with similar cells of origin, which is challenging using standard-of-care magnetic resonance imaging (MRI). This information can be invaluable in determining a surgical plan or avoiding surgery altogether in patients with an unidentified intracranial mass detected on MRI.



Nature Medicine 2020;26:1044–1047; https://doi.org/10.1038/s41591-020-0932-2

Emma Judson contributed to these reviews.