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MODERN PATHOLOGY

DICER1 mutations in embryonal rhabdomyosarcomas of the uterine corpus

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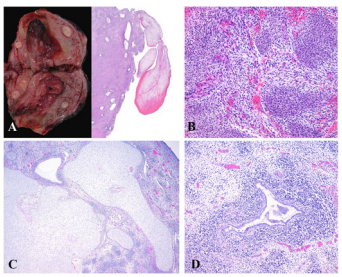
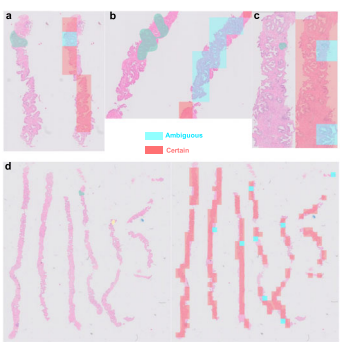


Bennett et al. characterized embryonal rhabdomyosarcomas of the uterine corpus (ucERMS) as a first step toward identifying possible triggers and therapeutic targets. The classic morphology was found in 16 of the 21 tumors examined: alternating hyper- and hypocellular areas of primitive small cells and differentiating rhabdomyoblasts in a loose myxoid/edematous stroma. The most frequent mutations detected were in *DICER1* (14/21), *TP53* (7/20), *PI3K/AKT*/mTOR pathway components (7/20), and *KRAS/NRAS* (5/20). In further analysis of ucERMS with *DICER1* mutations, 8 of the 14 showed concurrent loss of function and hotspot mutations in *DICER1*. As no patients had a known personal or family history of DICER1 syndrome, the group proposes that most DICER1-associated ucERMS are sporadic, but they cannot rule out the need to explore DICER1 further as a possible diagnostic marker/therapeutic target.

Supporting pathologists with automated IHC requests

https://doi.org/10.1038/s41379-021-00826-6

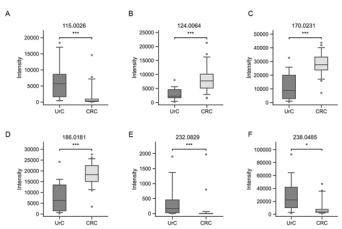


Immunohistochemistry (IHC) is a crucial diagnostic tool in circumstances where hematoxylin and eosin (H&E) morphology alone is not sufficient, but it causes delays in diagnosis. Chatrian et al. evaluated the potential implications of automating the request for IHC in prostate biopsy cases that contain ill-defined epithelial morphology. They developed an artificial intelligence tool that triggers IHC requests from assessment of the H&E slides so that a pathologist needs to view the case only once, when all required stains are done. It is estimated that this tool, with 99% accuracy and an average pathologist agreement of 0.81, could save an average of 11 min per case. Further validation might also allow the tool to be expanded to other cancer types.

LABORATORY INVESTIGATION

Developing tools to distinguish rare adenocarcinomas

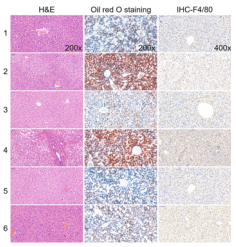
https://doi.org/10.1038/s41374-021-00612-7



Urachal adenocarcinomas (UrC) cannot be differentiated from other adenocarcinomas by histomorphology alone, and no reliable tissue-based diagnostic biomarkers are available. Accordingly, Neumann et al. took a multimodal approach, exploring the use of mass-spectrometry imaging-based metabolomics and digital pathology for diagnosis of UrC. The group developed machine-learning tools using matrix-assisted laser desorption/ionization (MALDI)-Orbitrap-mass spectrometry imaging (MSI) to determine metabolic differences between UrC and colorectal adenocarcinomas. They identified the antioxidant amino acid taurine as a potential biomarker for UrC, with a diagnostic accuracy much higher than that of any currently available technologies, such as immunohistochemistry of β-catenin or CK7.

Prostacyclin synthase in alcoholic liver disease

https://doi.org/10.1038/s41374-021-00531-7



Ethanol-mediated induction of gut endotoxin leakage and subsequent activation of macrophages play important roles in the pathogenesis of alcoholic liver disease (ALD). Macrophages exhibit different functional states and are classified as either classically activated (M1) or alternatively activated (M2). Pan et al. explored these functional states of macrophages and the mechanisms governing their polarization in ALD. They found that the anti-inflammatory enzyme prostacyclin synthase (PTGIS) was downregulated in a mouse model of ALD. Forced expression of PTGIS inhibited the macrophage switch to the M1 phenotype and promoted M2 polarization. PTGIS silencing promoted JAK/STAT1 activation in M1-polarized macrophages and inhibited JAK/STAT6 activation in M2-polarized macrophages, with interleukin-6 as the intervening regulator. Furthermore, PTGIS was downregulated via elevation of microRNA-140-3p.1 expression. The authors therefore determined that alternative activation of macrophages by prostacyclin synthase may ameliorate alcohol-induced liver injury and that PTGIS might be a therapeutic target for ALD.

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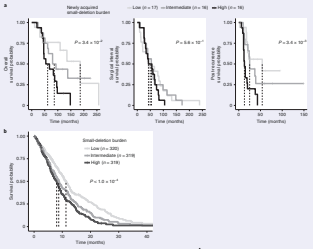
DNA repair in radiotherapy resistance

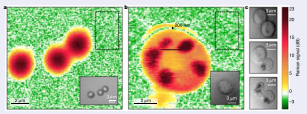
To assess the genomic impact of ionizing radiation used in cancer therapy, Kocakavuk et al. analyzed mutational spectra following radiotherapy (RT) in 190 paired primary and recurrent gliomas. Following RT, they detected aneuploidy and larger deletions that were genomically more dispersed. Mutational signature analysis implicated classical non-homologous end-joining-mediated DNA damage repair and mutagenesis of APOBEC enzymes due to RT. More significantly, though, worse clinical outcomes were associated with a high radiation-associated deletion burden. Therefore, the team proposes that effective repair of radiation-induced DNA damage is detrimental to patient survival and that their findings could be used to predict sensitivity to radiation therapy. Compounds that inhibit DNA repair may improve the response of cancer cells to RT. Numerous clinical and preclinical studies have shown efficacy in targeting DNA repair, which merits exploration to shed light on therapy resistance.



Nature Genetics 2021;53:1088–1096; https://doi.org/10.1038/s41588-021-00874-3

Novel microscope technology

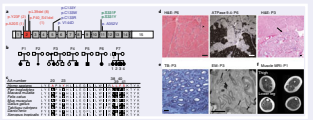
Microscopy remains a cornerstone of surgical pathology even in the era of molecular medicine. Microscope developers appreciate the changing needs of microscopists and have brought about some remarkable innovations. A recent paper in *Nature* describes a novel coherent Raman microscope that transcends the limitations of traditional light microscopes —specifically, the random nature of photons that constrain sensitivity, resolution, and speed. Increases in the intensity of the illumination can improve these only to a certain extent, given that bright lasers can severely disturb biological processes. The authors' coherent Ramen microscope utilizes quantum photon correlations to dramatically improve the signal-to-noise ratio of traditional light microscopes by 35% and offers subwavelength resolution. It allows visualization of biological structures that were not observable before, down to molecular bonds within a cell.



Nature 2021;594:201–206; https://doi.org/10.1038/s41586-021-03528-w

Excess sphingolipid synthesis causes childhood ALS

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with both sporadic and hereditary occurrences and varying ages of onset. Mohassel et al. explored four specific, dominantly acting *SPTLC1* variants in seven families manifesting as childhood-onset ALS. The group custom-designed small interfering RNAs that selectively target the *SPTLC1* ALS alleles for degradation, leaving the normal allele intact and maintaining normal sphingolipid levels in vitro. The variants disrupt the normal homeostatic regulation of serine palmitoyltransferase (SPT), a multisubunit enzyme that catalyzes the initial and rate-limiting step in sphingolipid biosynthesis. ORMDL proteins are responsible for homeostatic regulation of SPT activity, and the disruption in this homeostasis leads to elevated canonical SPT products. The group proposes that *SPTLC1* is a causative gene for ALS and that unrestrained sphingoid base synthesis is a metabolic mechanism.



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For a Chinese version of Inside the USCAP Journals, see the Supplementary Material.
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