Laboratory Investigation (2021) 101, 2–3

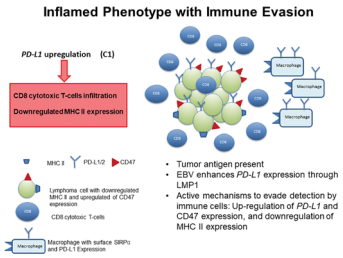
INSIDE THE USCAP JOURNALS

https://doi.org/10.1038/s41374-020-00521-1

MODERN PATHOLOGY

Immune landscape in DLBCL provides novel biomarkers

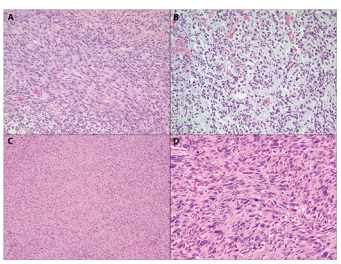
https://doi.org/10.1038/s41379-020-0616-y



El Hussein et al. reviewed newly published data that better describe the molecular characterization of diffuse large B-cell lymphoma (DLBCL), providing novel opportunities for diagnostic tools as well as treatment. Two large-scale whole-exome sequencing studies and a targeted hematologic malignancy-designed panel provided sources and opportunities for exploring established and novel biomarkers of DLBCL. The group reviewed elements including the germinal center reaction and the role of MYC expression in terminal B-cell differentiation. They explored both established and newly identified markers classifying DLBCL clusters, explaining the pronounced genomic heterogeneity in DLBCL. Inflamed DLBCL was found to be one of these new subsets, and the mechanisms for immune suppression was shown to be related to specific mutations and cytokine secretion, leading to T-cell infiltration. The group described genetic signatures associated with inflamed or immune excluded DLBCL, which may lead to alternative therapeutic directions for this heterogeneous disease.

Mesenchymal tumors of the GI tract, distinct from GISTs

https://doi.org/10.1038/s41379-020-0623-z

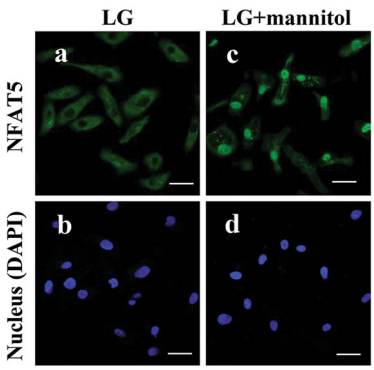


Atiq et al. evaluated a recent description of mesenchymal tumors in the gastrointestinal tract with *NTRK* fusions as gastrointestinal stromal tumors (GISTs) and found that it was not corroborated by their data. The group analyzed eight mesenchymal tumors involving *NTRK1* or *NTRK3* fusions across *TPM3–NTRK1* ($n = 3$), *TPR–NTRK1*, *LMNA–NTRK1*, and *ETV6–NTRK3* ($n = 2$), and *SPECC1L–NTRK3* in-frame gene fusions. The ages of the patients ranged from 2 months to 55 years; the tumors involved various portions of the gastrointestinal tract; and clinical outcomes varied, from relatively indolent to aggressive disease. The tumors were heterogeneous and were classified as infantile fibrosarcoma, low-grade CD34-positive S100 protein–positive spindle-cell tumors and unclassified high-grade spindle-cell sarcomas. The findings indicate the importance of interrogating *NTRK* alterations in any of these tumor types to distinguish them from GISTs during diagnosis.

LABORATORY INVESTIGATION

Hyperosmolarity regulates OSCC proliferation

https://doi.org/10.1038/s41374-020-00486-1

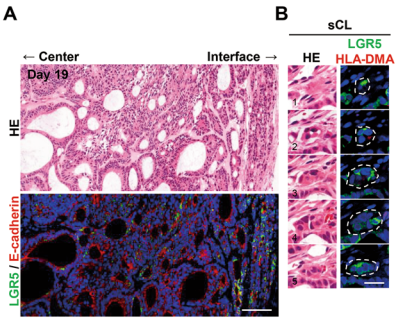


Epidermal growth factor receptor (EGFR) is highly expressed in several cancer types and is a common target for therapies, but cancer cells often become tolerant to these therapeutics. Yoshimoto et al. found that tumorigenicity of HSC-3 cells (human squamous cells) can be accelerated, depending on hyperosmotic stress in vivo. The group investigated osmolarity in the tumor microenvironment of oral squamous cell carcinoma (OSCC) and found that NFAT5 transcription factor has a functional role in enhancing proliferation. NFAT5 induced EGFR translocation from the endoplasmic reticulum to the plasma membrane through increased

expression of FPAGT1 via binding to the promoter region. This family of transcription factors has been shown to be highly expressed in OSCC and to regulate cancer cell proliferation. The authors propose that the findings may indicate a potential therapeutic target for OSCC.

Cancer stem cells at leading edge of cancer growth

https://doi.org/10.1038/s41374-020-0471-y



Yamazaki et al. explored the role of cancer stem cells (CSCs) in the tumor hierarchy with regard to tumor growth. Using a previously generated antibody against LGR5, a known CSC marker in colorectal cancer, in xenograft and three-dimensional culture models, the group explored the interactions of these cells and observed them aggregating into small clusters (sCLs) over the course of tumor growth. The LGR5-positive sCLs formed continuously in the invasive front, implicating them in tumor growth and expansion of CSCs. To validate the findings, the authors identified the same sCLs with high LGR5 expression in clinical samples and concluded that sCLs play a unique role in tumor growth and perpetuation of CSCs. Exploring this further could lead to potential therapeutic targets against these CSCs.

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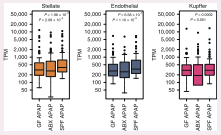
Regulation of acute liver failure may lead to therapeutic design

Acute liver failure (ALF) is a resulting complication in multiple etiologies, and its treatment is limited mainly to supportive care and ultimately liver transplantation.

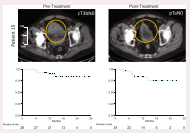


Using two models of ALF, Kolodziejczyk et al. elucidated the unique pattern of cellular involvement and intercellular crosstalk that they believe drive ALF. They investigated an MYC-dependent transcriptional program involved in cellular activation during ALF, regulated by the gut microbiome through Toll-like receptor (TLR) signaling. Upregulation of Ccl2, the key chemokine promoting monocyte recruitment, may also lead to impairment of Ly6C-positive monocyte infiltration in ALF. The group's data also showed that MYC is upregulated in human ALF patients as compared with controls, and they propose that pharmacological inhibition of MYC, upstream of TLR signaling, might ameliorate ALF-induced hepatic damage. The findings suggest novel targets for therapeutic intervention, including even the MYCi and P38 inhibitors used in cancer research.

Nature Medicine, published online 26 October 2020; https://doi.org/10.1038/s41591-020-1102-2

Neoadjuvant PD-L1 plus CTLA-4 blockade in urothelial carcinoma

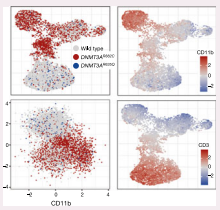
Gao et al. discuss the results of a pilot study of combination neoadjuvant anti-PD-L1 (durvalumab) plus anti-CTLA-4 (tremelimumab) in cisplatin-ineligible urothelial carcinoma, with all patients defined by bulky tumors, variant histology, lymphovascular invasion, hydronephrosis, and/or high-grade upper tract disease. The primary endpoint was safety, and there were immune-related adverse events ≥grade 3 in 6 of 28 patients, including laboratory abnormalities, hepatitis, and colitis. After surgery, there was a pathological complete response rate of 37.5% and downstaging to pT1 or less in 58%. When exploring the biomarkers, the group examined mutational signatures, treatment-related suppressive markers, and a tertiary lymphoid signature of four genes found to be significantly higher in responders than in nonresponders. They believe their data support further development of the protocol and additional subjects to better explore it in patients with localized urothelial carcinoma without established standard-of-care neoadjuvant therapeutics.



Nature Medicine, published online 12 October 2020; https://doi.org/10.1038/

Delineating clonal evolution through single-cell mutation analysis

Molecular profiling has suggested that mutations in acute myeloid leukemia (AML) are acquired in a stepwise progression—mutant genes with high variant allele frequencies appear early in leukemogenesis and lower variant allele frequencies later. To further delineate the clonal framework and distinguish which mutations occur within the same clone(s), Miles et al. performed single-cell mutational profiling and demonstrated that AML is dominated by a small number of clones, frequently exhibiting co-occurring mutations in epigenetic regulators. The group mapped clonal trajectories for each sample and uncovered combinations of mutations that synergized to promote clonal expansion and dominance. They also mapped somatic genotype and clonal architecture with immunophenotype. Clonal complexity evolves with disease progression, and this may provide its own opportunities for therapeutic development aimed at intercepting clonal evolution and/or targeting cancer as a multiclonal disease.



Nature 2020;587:477–482; https://doi.org/10.1038/s41586-020-2864-x

Emma Judson contributed to these reviews.