Modern Pathology (2021) 34, 1042–1043

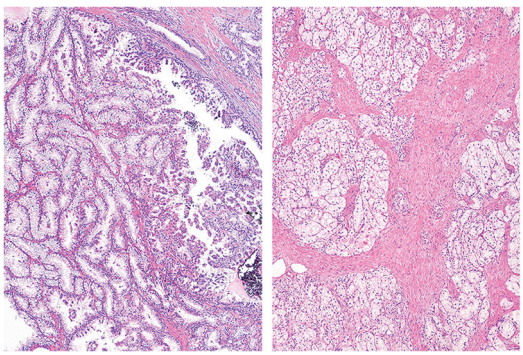
INSIDE THE USCAP JOURNALS

https://doi.org/10.1038/s41379-021-00812-y

MODERN PATHOLOGY

Improved classification of renal cell carcinoma

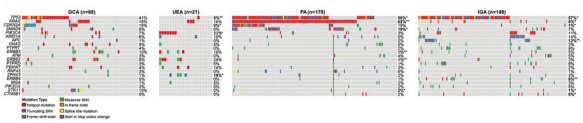
https://doi.org/10.1038/s41379-021-00737-6



The Genitourinary Pathology Society sought to characterize specific molecular features associated with morphologies or patterns of morphologies and corresponding immunohistochemical profiles in renal neoplasia. Given the importance of diagnosis and the impact on therapeutic options and predicted outcomes, improved recognition and exploration of these trends can facilitate improved patient care in the future and reduce the number of samples in the category "unclassifiable renal carcinomas/tumors." Trpkov et al. proposes three novel entities: eosinophilic solid and cystic renal cell carcinoma (ESC-RCC), anaplastic lymphoma kinase rearrangement–associated renal cell carcinoma (ALK-RCC), and renal cell carcinoma with fibromyomatuous stroma (RCC FMS). They hope that improved recognition of the increasing spectrum of novel renal entities will allow pathologists to more accurately diagnose, manage, and prognose individual patients with RCC.

Therapeutic targets for gastric-type cervical adenocarcinoma

https://doi.org/10.1038/s41379-020-00726-1

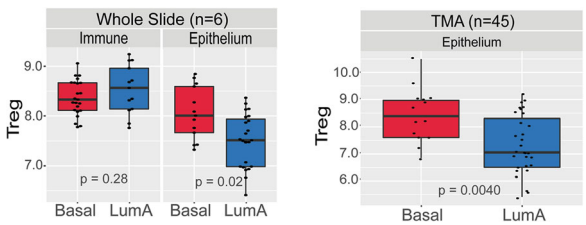


Selenica et al. investigated genetic alterations in a large cohort of gastric-type cervical adenocarcinoma (GCA) and compared them with several other known cancer types. GCAs are characterized by mucinous morphology, gastric-type mucin, lack of association with human papillomavirus, and treatment resistance. The ability to distinguish their pathology from other similar cancers and determine possible therapeutic targets is key to improving treatment options for these patients. Massively parallel sequencing targeting 410–468 cancer-related genes was performed, revealing somatic mutations and copy number alterations. Somatic mutations in *TP53*, *CDKN2A*, *KRAS*, and *STK11* were the most common ones, and those in *ERBB3*, *ERBB2*, and *BRAF* were thought to be potentially targetable. Mutations in genes such as *STK11* were proposed as biomarkers of GCAs that could distinguish them from other adenocarcinomas with similar morphology in metastasis, whereas *ERBB3/2* are proposed as therapeutic targets.

LABORATORY INVESTIGATION

Immune profiles distinguish between breast cancer pathologies

https://doi.org/10.1038/s41374-020-00506-0

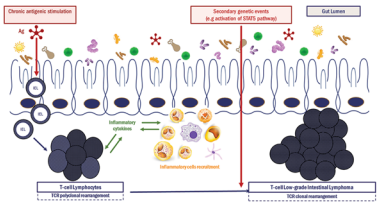


To elucidate the role of tumor-infiltrating lymphocytes in basal-like vs. luminal breast cancer, Walens et al. used the GeoMx® (NanoString) platform to perform digital spatial profiling of immune-related proteins in whole-tumor sections along with tissue microarrays (TMAs). After increasing the biomarkers to 44 antibodies from the limited number assessed in previous studies, the group was able to isolate hot spots of CD45 expression that also exhibited many immune markers, and they interpreted a diverse and robust immune response. Regulatory T-cell markers (CD4, CD25, and FOXP3) were expressed more highly in basal-like than in luminal breast cancer. The

authors propose that TMAs are a viable approach for obtaining important immunoprofiling data and ultimately plan to combine TMAs with genomic datasets. These immune markers may therefore have prognostic and targetable impact for the treatment of breast cancer patients.

Novel natural models in oncology

https://doi.org/10.1038/s41374-021-00581-x



Freiche et al. performed a prospective study to determine whether feline low-grade intestinal T-cell lymphoma (LGITL) might serve as a model of human indolent T-cell lymphoproliferative disorder of the gastrointestinal tract (GI-TLPD). Histopathological and molecular studies were performed on small intestinal biopsies from 22 domestic cats with LGITL located in the jejunum. The small intestinal lamina propria was infiltrated by large numbers of small $CD3^+$ T-cell lymphocytes with various CD4 and CD8 expression profiles. Intraepithelial lymphocyte (IEL) counts were elevated in all cases. Ki67 was expressed in lymphocytes in lamina propria and in IELs at a low level (<30%). Expression of phosphorylated STAT5 without CD56 and phosphorylated STAT3 was shown in the majority of LGITLs, and T-cell receptor gamma chain gene monoclonality was found in 86% of cases. The group confirmed the relationship between feline LGITL and human GI-TLPD and propose its use as a relevant model of human disease, opening the door to use of spontaneous pet models in oncology.

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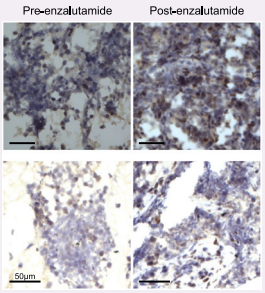
Exploring therapeutic resistance

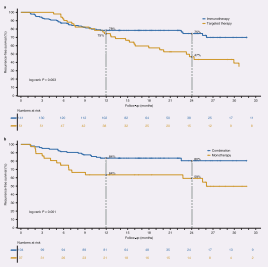
Treatment resistance is a common hurdle in cancer therapeutics. He et al. saw metastatic castration-resistant prostate cancer (NEPC) as a model for the study of the mechanisms of this resistance. Using single-cell transcriptomes from 14 patients with advanced prostate cancer, representing all common metastatic sites, the group demonstrated that—irrespective of treatment exposure—adenocarcinoma cells pervasively co-expressed multiple androgen receptor isoforms. Resistance to enzalutamide was associated with cancer cell–intrinsic epithelial–mesenchymal transition and transforming growth factor-β signaling. A subset of the tumors also expressed dysfunction markers on cytotoxic $CD8^+$ T cells undergoing clonal expansion following enzalutamide treatment, although in some patients *PDCD1* expression suggests that in some tumors $CD8^+$ T cells do mount an antitumor response in the context of enzalutamide exposure. The authors identified a target pathway for further investigation to better characterize cytotoxic cells and their potential as therapeutic targets in NEPC.



Nature Medicine 2021;27:426–433; https://doi.org/10.1038/s41591-021-01244-6

Pathological response as an early surrogate in melanoma therapeutics

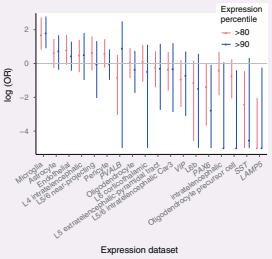
Seeking to elucidate the association between pathological response, recurrence-free survival, and overall survival with neoadjuvant therapy in melanoma, Menzies et al. pooled data from six clinical trials (a total of 192 patients) of BRAF/MEK targeted therapy (51 patients) and anti-PD-1-based immunotherapy (141 patients). A pathological complete response occurred in 40% of patients (47% with targeted therapy and 33% with immunotherapy) and correlated with improved recurrence-free survival and overall survival. In immunotherapy patients with pathological complete response, near pathological complete response, or partial pathological response, very few relapses were seen, and no patient had died as of the time the paper was written. With pathological complete response from targeted therapy, the 2-year recurrence-free survival and overall survival were 79% and 91%, respectively. The data indicate the importance of using pathological response as an early surrogate for outcome in clinical trials for melanoma as it already is for breast, gastroesophageal, and anal cancers, among others.



Nature Medicine 2021;27:301–309; https://doi.org/10.1038/s41591-020-01188-3

Seeking causal gene loci for Alzheimer's disease

There are known genomic loci that associate with Alzheimer's disease (AD), but connecting the genes with causal features of the disease is far from complete. Schwartzentruber updated the genome-wide AD meta-data analysis and identified 37 risk loci, including *CCDC6*, *TSPAN14*, *NCK2*, and *SPRED2*. Using three single-nucleotide polymorphism (SNP)-level fine-mapping methods, the group identified 21 SNPs that each had a >50% probability of being causally involved in AD risk. Colocalization analysis across 109 gene expression traits and comparison of the data revealed an additional five loci: *BIN1*, *APH1B*, *PTK2B*, *PILRA*, and *CASS4*. Of 18 broad cell-type clusters, only microglia showed clear enrichment of AD risk near genes with expression above the 90th percentile across cell types. The data provide evidence of diverse mechanisms in AD pathogenesis and target genes for therapeutic development.



Nature Genetics 2021;53:392–402; https://doi.org/10.1038/s41588-020-00776-w

Emma Judson contributed to these reviews.

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Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41379-021-00812-y.