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MODERN PATHOLOGY

Diagnostic discernment for diseases that require distinct therapeutics

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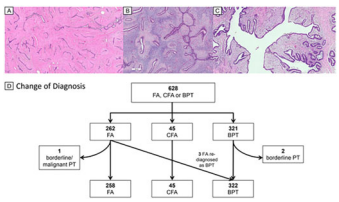

Histological review of fibroadenomas and benign phyllodes tumors reveals the morphological heterogeneity that can make diagnosis challenging, so Ng et al. explored employing histology in conjunction with cancer driver mutations. Utilizing 262 conventional benign fibroadenomas (FAs) and 321 benign phyllodes tumors (PTs) from the International Fibroepithelial Consortium, the team explored breast fibroepithelial lesions. Benign PTs had a higher mutational burden, including a higher rate of cancer driver alterations, with mutations in *MED12, TERT2* promoter, and *EGFR*; those with *MED12* mutations were more likely to have mutations in the *TERT* promoter, *RARA, SETD2* and *EGFR*. There was little to differentiate between FAs and cellular FAs, other than *PIK3CA* and *MAP3K1*. *TERT* promoter alterations were identified as the most discriminating way to distinguish FAs and benign PTs. This study highlights the importance of next-generation sequencing to improve diagnostic discernment between similar diseases that require distinct therapeutics.

Molecular distinction between primary and secondary glioblastomas

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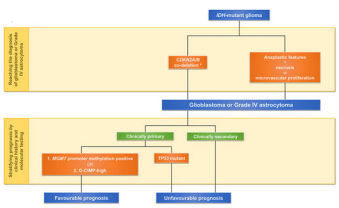

Glioblastomas can be classified into *IDH*-mutant and *IDH*-wild type, with a better prognosis for the former. Seeking to examine *IDH*-mutant primary glioblastomas, Wong et al. recruited 67 patients to assess the correlation between molecular findings and clinical parameters. Median survival was statistically better for *IDH*-mutant primary glioblastomas than *IDH*-wild type and *IDH*-mutant secondary glioblastomas in the datasets, and typical molecular features (*EGFR* amplification and TERT promoter mutations) were seen in only a few of the 67 primary tumors. The authors examined clinical parameters and found that G-CIMP-high status and *MGMT* promoter methylation were independent good prognosticators of overall survival, while *TP53* mutation indicated a poor prognosis. The group concludes that *IDH*-mutant primary glioblastomas have significant molecular differences from secondary glioblastomas and have identified specific prognostic markers.

LABORATORY INVESTIGATION

Machine learning and metabolomics in a breast cancer progression model

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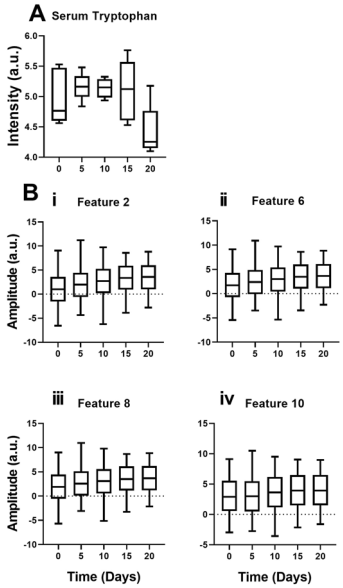

Rodrigues et al. set out to bring photoacoustic spectroscopy, machine learning and a breast tumor xenograft model together to better understand breast tumor progression. At specific time points the ex-vivo tumors were excited with 281 nm pulsed laser light and the corresponding photoacoustic spectra were recorded. Using MATLAB, the spectra were pre-processed and analyzed, and the top 10 features from each time point were selected based on their prediction ranking values using the mRMR algorithm. Support Vector Machine-

based algorithms were then employed to the chosen features and high accuracy was demonstrated across multiple analyses. The group went on to demonstrate a decrease in serum tryptophan levels at progressive time points that inversely correlated with the spectral features labeled as 2, 6, 8 and 10 during disease progression. Though this is the first in its field, the method could have clinical implications for early detection of breast cancer.

Improving assessment of gestational age from placental imaging using deep learning

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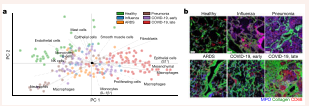
Given the crucial functions the placenta plays in a developing pregnancy and the influence an abnormal placenta can have in gestational abnormalities, a better way to utilize data from placental sections would be beneficial. Mobadersany et al. developed *GestAltNet* to provide a machine learning-based assessment that emulates human attention to high-yield areas and aggregation for numerous samples. By discriminating areas of terminal villi from other placental structures, their system was able to predict gestational age more accurately from placental slides when compared with a baseline model. Embracing the assertion that villous maturation is machine-recognizable, the group proposed that their system could support the study of abnormalities in villous maturation as seen in gestational diabetes and preeclampsia. While this is unlikely to replace existing methods of ultrasound to determine gestational age, it could be useful in cases where dating is unclear or there are other discrepancies.

nature.com/pathology

Exploring lung pathology during COVID-19 progression

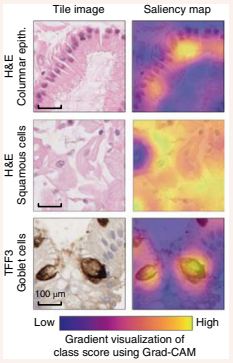
Rendeiro et al. investigated the interplay between infected cells and the immune system at sites of COVID-19 infection using high-parameter imaging mass cytometry to target expression of 36 proteins at a single-cell resolution. Extensive immune infiltration (neutrophils and macrophages) was revealed, in conjunction with the disordered structure of the infected lung. COVID-19 was shown to predominantly infect alveolar epithelial cells and induce a localized hyperinflammatory state that is linked to lung damage. Increased macrophage extravasation and increased numbers of mesenchymal cells and fibroblasts were seen with increased proximity, perhaps as a result of attempts to repair the damage. The group proposes that early immunological interventions that suppress excessive complement activation could have a therapeutic benefit in COVID-19 patients.



Nature 2021; https://doi.org/10.1038/s41586-021-03475-6

Deep learning to improve early detection of esophageal adenocarcinoma

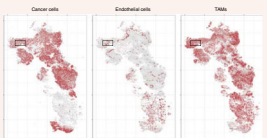
Combining expert knowledge and existing clinical decision pathways with deep learning methods presents a challenge that Gehrung et al. sought to tackle. The developed a deep learning framework that took data from two clinical trials and analyzed 4,662 pathology slides from 2,331 patients to detect Barrett's esophagus, a known and predominant precursor of esophageal adenocarcinoma. Established pathology protocols were used to triage samples into eight classes, and by automating the review of the lower-priority classes, the group proposes a potential 57% workload reduction for human pathologists, while matching their diagnostic performance. Such workload reduction may lead to an increase in diagnostic quality and confidence.



Nature Medicine 2021; https://doi.org/10.1038/s41591-021-01287-9

Targeting the immune landscape of glioblastoma by stage of disease

Antunes et al. set out to better understand the dynamics of malignancy-controlling myeloid cells during glioblastoma (GBM) disease progression using sing-cell RNA sequencing and CITE-sequencing in mouse tumors and in human patients. Several features were found to be conserved across species and dynamic across disease stages. Microglia- and monocyte-derived tumor-associated macrophages (TAMs) were self-renewing populations that competed for space. Microglia-derived TAMs were predominant in newly diagnosed tumors but were outnumbered by monocyte-derived TAMs following recurrence. Targeting these specific TAMs at the right stage in the progression of GBM holds potential as a therapeutic breakthrough.



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Emma Judson contributed to these reviews.
For a Chinese version of Inside the USCAP Journals, see the supplementary material.

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