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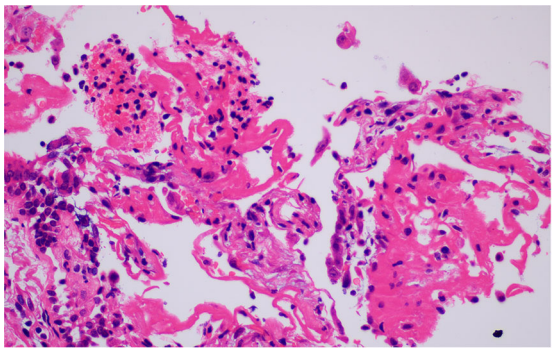
MODERN PATHOLOGY

COVID-19 postmortem core biopsies

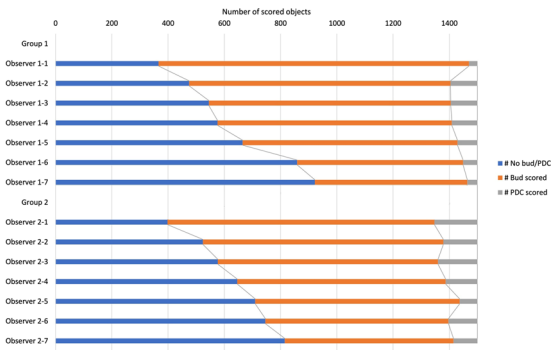
https://doi.org/10.1038/s41379-020-0536-x



To determine the pathology that may contribute to progression and fatality of COVID-19 pneumonia, the authors performed postmortem needle-core biopsies of lung, liver, and heart from four patients who died from the disease. All patients had elevated white blood cell counts. Histologically, the lungs showed injury to the alveolar epithelial cells, hyaline membrane formation, and hyperplasia of type II pneumocytes, all components of diffuse alveolar damage. Consolidation by fibroblastic proliferation with extracellular matrix and fibrin forming clusters in airspaces was also evident. Bacterial pneumonia was found in some patients. Changes in the liver and heart were observed but likely were secondary or related to underlying diseases.

Removing interobserver bias by teaching a computer

https://doi.org/10.1038/s41379-019-0434-2



As is often the case with immunohistochemistry-based assays, interobserver variability proves to be the most challenging aspect of the readout. Bokhorst et al. sought to develop computer algorithms that could unequivocally identify tumor budding using a large-scale, international, digital observer study. From a pool of 46 colorectal cancer cases with tumor budding, 3000 tumor bud candidates were selected based on digital image-analysis algorithms, and members of an international tumor budding consortium were asked to categorize the resulting images. Complete agreement by all seven observers was reached for only 34% of the 3000 tumor bud candidates, with 59% agreed on by five of the observers. This gave the group the data that they needed to propose a machine-learning approach as an essential tool for evaluating tumor budding more thoroughly.

LABORATORY INVESTIGATION

New biomarker for glioblastoma and possible therapeutic target

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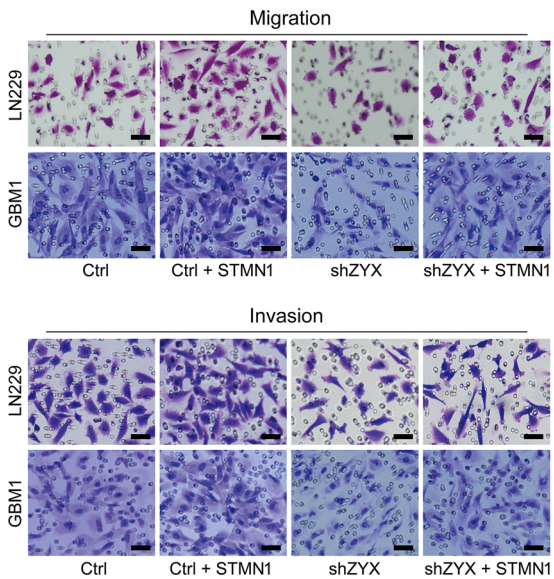
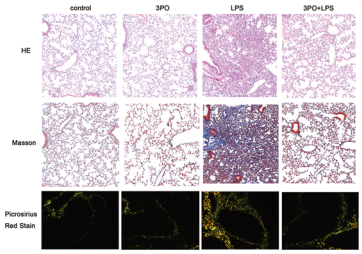


Wen et al. sought to validate zyxin (ZYX) as a biomarker of aggressive human glioblastoma multiforme (GBM). Using multiple cohorts of glioma patients, the group showed that *ZYX* expression correlated with tumor progression and poor prognosis, and they went on to demonstrate its role in invasion and growth. They showed that stathmin 1 (*STMN1*) was a potential target for ZYX, with ZYX regulating *STMN1* protein levels. This axis was shown to be more complex than a simple direct interaction due to the

location in the cell of each protein, and the authors believe that other mediators may yet need to be identified. STMN1 itself was shown to promote invasion of GBM cells as well as rescue the invasion repression caused by *ZYX* loss. Identifying biomarkers that speak to aggressive phenotypes of disease is often key to early detection and can lead to potential therapeutic targets.

A novel pathway for lipopolysaccharide-induced pulmonary fibrosis development

https://doi.org/10.1038/s41374-020-0404-9



Metabolic reprogramming is a wide field, having been shown to play a critical role in many diseases. Hu et al sought to investigate a gap in the knowledge base and investigate the role lipopolysaccharide (LPS) plays in lung fibrosis. They found that LPS promotes collagen synthesis through aerobic glycolysis via activation of the PI3K-Akt-mTOR pathway, leading to expression of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase3 (PFKFB3). Furthermore, inhibiting any element along the pathway was sufficient to reverse the phenomena. A mouse model of LPS-induced pulmonary fibrosis was used to show that PFKFB3 expression and aerobic glycolysis were also detected in vivo. The PI3K-Akt-mTOR/PFKFB3 pathway is thus a potential therapeutic target in cases of LPS-induced pulmonary fibrosis.

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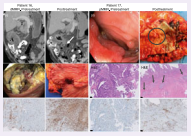
A new standard of care for a defined group of colon cancer patients?

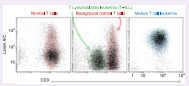
In an exploratory clinical trial (ClinicalTrials.gov: NCT03026140), 40 patients with mismatch repair (MMR)-deficient (dMMR) and 20 with MMR-proficient (pMMR) colorectal cancer were given adjuvant immunotherapy (one dose of ipilimumab and two doses of nivolumab, with or without celecoxib, or two doses of nivolumab). Treatment was well tolerated, and all patients underwent radical resections without delays. Of the patients who received ipilimumab + nivolumab (20 dMMR and 15 pMMR tumors), 35 were evaluable. All 20 of the dMMR patients in that group showed pathological response, with 19 showing <10% residual tumor and 12 pathological complete responses. In pMMR tumors, 4 of 15 showed pathological responses. Of the pMMR patients who responded, $CD8^{+}PD\text{-}1^{+}$ T-cell infiltration was predictive; if validated in a larger cohort, this might help in selecting patients with pMMR tumors for future neoadjuvant immune-checkpoint inhibition studies. The authors propose that neoadjuvant immunotherapy may have potential as the standard of care for this defined group of colon cancer patients.



Nature Medicine, 2020;26:566–576; https://doi.org/10.1038/s41591-020-0805-8

Automated diagnosis of hematopoietic diseases*

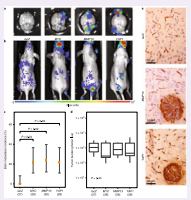
Tsai et al. sought to develop a high-throughput, highly multiplexed, single-cell assay that would combine the work of the hematopathologist and cell surface expression analysis by empowering mass cytometers to "see" like pathologists. A test group of 71 diverse clinical samples was used to test their protocols, and it was shown that the assay could determine a robust and distinct pattern of morphometric markers for the identifiable cell types. Lamin-B1 could be used to highlight acute leukemias, lamin-A/C could distinguish between normal and neoplastic T-cells, and VAMP-7 recapitulates light-cytometric side scatter. It was also shown that the assay could outperform flow cytometry and comparable expert microscopy when recalibrated for myelomonocytic blast enumeration, reducing the need for years of specialized training. The authors propose that their system, incorporating traditional surface markers with machine learning, provides the scope for automated diagnosis of complex hematopoietic diseases.



Nature Medicine, 2020;26:408–417; https://doi.org/10.1038/s41591-020-0783-x

Identification of novel drivers of lung cancer metastasis to the brain

Patient mortality from lung adenocarcinoma (LUAD) is frequently due to brain metastases (BM-LUAD). Shih et al., seeking to identify potential genomic drivers that promote this metastasis to the brain, performed whole-exome sequencing of 73 cases of BM-LUAD. Using LUAD as the control, the group showed that three candidate genes were apparent, including *MYC* (12% versus 6%), *YAP1* (7% versus 0.8%) and *MMP13* (10% versus 0.6%), and significantly more frequent deletions in *CDKN2A/B* (27% versus 13%). After validating their findings using an independent cohort, they functionally assessed the candidates in patient-derived xenograft models, validating overexpression of each increased incidence of brain metastasis. Their findings show that somatic alterations contribute to brain metastases and validate the concept of using genomic sequencing to identify these candidate genes. These genes then become potential therapeutic targets for prevention and treatment of metastasis.



Nature Genetics, 2020;52:371–377; https://doi.org/10.1038/s41588-020-0592-7

Emma Judson contributed to these reviews.