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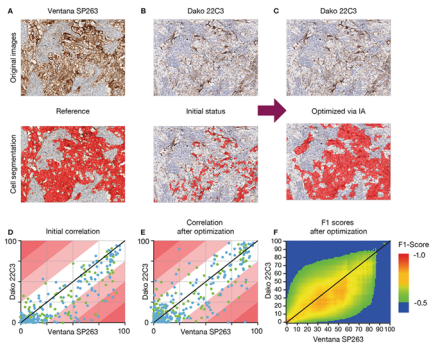
https://doi.org/10.1038/s41379-020-0502-7

MODERN PATHOLOGY

Automated image analysis of PD-L1

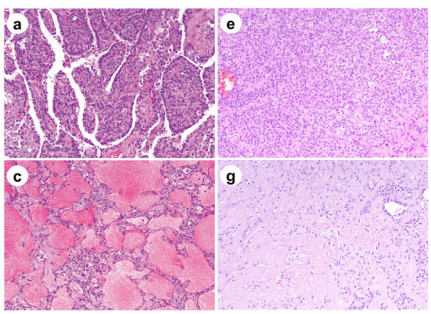
https://doi.org/10.1038/s41379-019-0349-y



Widmaier et al. developed a computer-aided automated image analysis technique with a customized programmed cell death ligand-1 (PD-L1) scoring algorithm to determine comparability across PD-L1 immunohistochemistry (IHC) assays. They compared this system with manual pathologist scores. Taking four IHC PD-L1 assays (clones SP263, SP142, 22C3, and 28-8), the group used their image analysis scoring algorithm to quantify the percentage of PD-L1-positive tumor cells on scans of whole-slide images of archival tumor samples, being careful that scans were restricted to comparable tissue areas. Reference pathologist scores were used as a baseline. Overall, the four assays were highly concordant. For 471 PD-L1-evaluable samples, the image analysis and pathologist scores were highly concordant, with F1 scores from 0.8 to 0.9. The authors propose their assay as a supportive tool to pathologists in a clinical setting.

AKT1 mutations in sclerosing pneumocytoma

https://doi.org/10.1038/s41379-019-0357-y

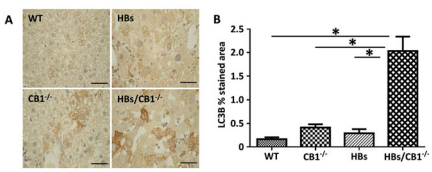


Sclerosing pneumocytoma is a unique, benign neoplasm of the lungs with no clear molecular alteration implicated as a driver. A prior whole-exome-sequencing study identified activating *AKT1* point mutations in about half the cases tested; no oncogenic mutations were identified in the remaining samples. In this present work, Yeh et al. identified internal tandem duplications in the *AKT1* gene in 22 of 44 tested samples (50%). These duplications were mutually exclusive with activating point mutations in the same gene. The internal tandem duplications resulted in duplications of 7–16 amino acids in the Pleckstrin homology domain of the AKT1 protein, crucial for its activation. Taking into account this new duplication finding, activating *AKT1* mutations were identified in almost all the sclerosing pneumocytomas in the study (41 of 45, 93%), validating and extending this molecular hallmark of the disease.

LABORATORY INVESTIGATION

Identifying an essential step in lipid breakdown

https://doi.org/10.1038/s41374-019-0327-5

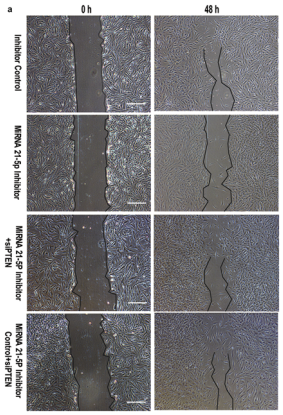


While researching the endocannabinoid (EC) system as it relates to the pathogenesis of metabolic diseases, Irungbam et al. explored the modulatory effect of endocannabinoid receptor 1 (CB1) signaling on perilipin 2 (PLIN2)-mediated lipophagy. Knockout of the CB1 gene ($CB1^{-/-}$) reduced expression of the lipid droplet binding protein PLIN2. Activation/antagonization of CB1 in cell cultures caused induction/reduction of PLIN2, respectively, and this decreased expression was associated with suppression of lipogenesis and triglyceride synthesis. The findings suggest that loss of CB1 signaling leads to reduced PLIN2 abundance, which triggers lipophagy and implicates this process as an essential step in lipid breakdown. The association between CB1 signaling and PLIN2 may stimulate translational studies analyzing new

diagnostic and therapeutic options for nonalcoholic fatty liver disease and other metabolic diseases.

miRNA and *PTEN* in keloidal scars

https://doi.org/10.1038/s41374-019-0323-9

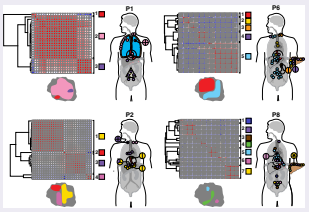


Yan et al. investigated the underlying mechanisms of electron beam (EB) irradiation in reducing recurrence of keloids and found that with increasing apoptosis, EB irradiation inhibits autophagy in keloid fibroblasts by reducing miR-21-5p, which itself regulates migration and LC3B expression via *PTEN/AKT* signaling. Using microarray and immunohistochemistry assays as well as in vitro scratch-wound healing migration assays and knockdown models for miR-21-5p antagonism and *PTEN* RNA interference, the group identified a potential mechanism wherein miR-21-5p inhibition regulates autophagy and migration in EB-irradiated keloid fibroblasts, preventing recurrence after treatment. They propose miR-21-5p inhibition as a possible new therapeutic target to control keloid relapse, perhaps mimicking the effects of EB radiation.

nature.com/pathology

Diaspora model of metastatic spread

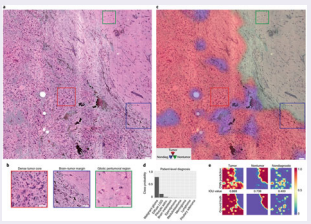
Poor outcomes in advanced esophageal adenocarcinoma (EAC) indicated an opportunity to explore the pattern and timing of metastatic spread. Data from whole-genome sequencing and phylogenetic analysis showed that in the majority of 388 samples (90%) from 18 individuals with EAC, multiple subclones from the primary tumor spread very rapidly. Noorani et al. have termed this "clonal diaspora." Their identification of this tendency toward early simultaneous seeding of oligometastases runs counter to the linear progression seen in prostate cancer, in which seeding seems to occur in waves. The authors demonstrated that a single clone had potential to seed multiple metastatic sites and that subclonal spread was not limited by location or tissue type. They note the need for future research into whether this clonal diasporal pattern might be seen in other cancer types.



Nature Genetics 2020;52:74–83; https://doi.org/10.1038/s41588-019-0551-3

Artificial intelligence for intraoperative brain tumor diagnostics

Hollon et al. sought a more streamlined process for intraoperative diagnosis during cancer surgery. They explored a combination of stimulated Raman histology (SRH) and deep convolutional neural networks (CNNs) to predict diagnosis bedside in near real time using automation. The CNNs, trained to recognize 2.5 million SRH images, predicted brain tumor diagnosis in the operating room in under 150 seconds, compared with the existing frozen-section methods that routinely take 20–30 minutes). In a multicenter prospective clinical trial ($n = 278$), the authors showed that the diagnostic accuracy of their method matched that of conventional histological methods (94.6% versus 93.9%, respectively). Their CNNs were trained to recognize different classes of tumor and normal tissue in order to facilitate intraoperative decision-making in significantly less time than conventional pathology, potentially improving the ability to adapt the scope of surgery to the case at hand in real time.



Nature Medicine 2020;26:52–58; https://doi.org/10.1038/s41591-019-0715-9

Nature Medicine: looking forward to the next quarter-century

On the occasion of its 25th anniversary, *Nature Medicine* asked thought leaders and experts what will shape the next 25 years of medical research. Their responses ranged from the "bigness" of the datasets produced by genome-wide association studies to the rising profile of gene therapy and progress in treating disease at its genetic roots. Some noted how precision medicine and genetics has enabled advances in preventive care, cancer vaccines, and other areas, leading to a rise in life expectancy. Culture and demographics featured strongly; precision medicine and changing cultures will drive growth and improvement to economies as well as individuals, to change not only medicine but the world stage with a yet-to-be-designed planetary health infrastructure. Also discussed were the aging population and the need to improve our relationship with aging. The next 25 years will be eye-opening.

Nature Medicine 2019;25:1804–1807; https://doi.org/10.1038/s41591-019-0693-y

Emma Judson contributed to these reviews.