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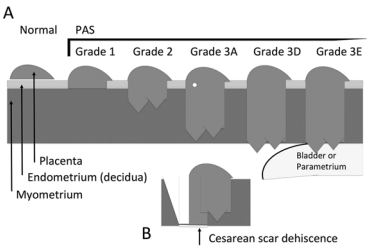
MODERN PATHOLOGY

Unifying terminology for PAS

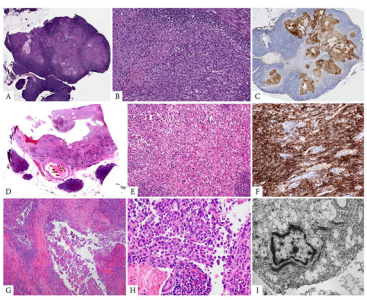
https://doi.org/10.1038/s41379-020-0569-1



A panel of experts discussed reporting guidelines with the aim of bringing uniformity to a currently inconsistent set of terminology and diagnostic criteria for placenta accreta spectrum (PAS) disorders. The proposed system includes stratification and terminology for specific elements across the PAS spectrum to encompass more of the guidelines of the International Federation of Gynaecology and Obstetrics (FIGO). Terms were incorporated for delivered placenta, total or partial hysterectomy with or without extrauterine tissues, curetting for retained products of conception, and, in a controversial decision, separating hysterectomy specimens from those for delivered placentas. The impact of unifying terminology in this context will support the clinical sphere as a whole, allowing clearer diagnoses and clinical plans.

Investigating a novel malignant phenotype

https://doi.org/10.1038/s41379-020-0646-5

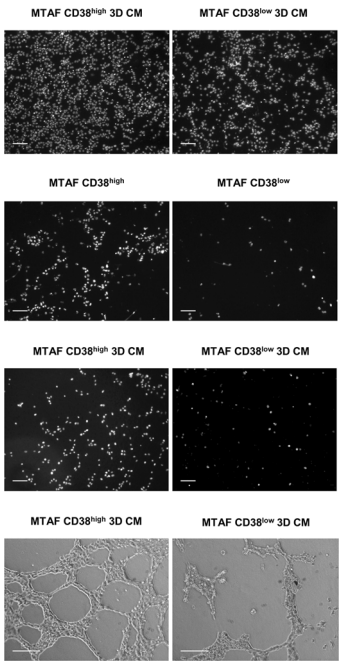


Argani et al. describe their investigation into a novel malignant epithelioid neoplasm with an immunophenotype suggesting epithelial differentiation. In a group of 13 previously unclassified epithelioid neoplasms, the defining feature was *EWSR1/FUS–CREB* fusion events. All showed predominantly epithelioid morphology associated with cystic or microcystic changes, except for one that expressed EMA and/or CK. Five were positive for WT1 but negative for melanocytic and mesothelioma markers. Eleven of 13 cases showed CREM-related fusions (*EWSR1–CREM 7* and *FUS–CREM 4*) and the other two harbored an *EWSR1–ATF1* fusion. Malignant potential was confirmed when 7 of the 13 patients presented with and/or developed metastases. This new entity therefore straddles the features between angiomatoid fibrous histiocytoma and mesothelioma, although the investigators acknowledge the need for increased class sizes to further define the relationship of this group to other tumors with these fusions.

LABORATORY INVESTIGATION

CAF-CD38 fosters tumorigenesis

https://doi.org/10.1038/s41374-020-0458-8

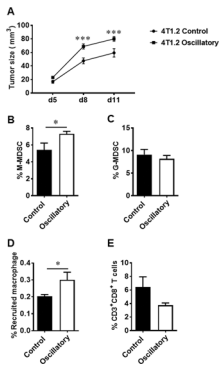


Investigations into progression of primary and metastatic melanoma led Ben Baruch et al. to examine the local microenvironment and the influence of cancer-associated fibroblasts (CAFs). Having previously reported that CD38 participates in melanoma growth and metastasis, in this paper they demonstrate its pro-tumorigenic functions. CD38-deficient fibroblasts with B16F10 melanoma cells limited tumor size compared with CD38-expressing fibroblasts, in which migration was promoted toward melanoma cells. The group demonstrated that CAF-CD38 drives protein expression, including VEGF-A, FGF-2, CXCL-12, MMP-9, and HGF; illustrating an angiogenic/pro-metastatic (pro-invasion

and migration) signature. CD38 fibroblasts may therefore be a viable therapeutic target, and the effectiveness of this research might not be limited to cancer given the association of these features in fibrosis and inflammatory diseases.

How mechanical strain influences immunosuppression in TME of BCa

https://doi.org/10.1038/s41374-020-0452-1



Wang et al. investigated mechanical forces within the tumor microenvironment (TME) of developing breast cancer (BCa) tumors and demonstrated that mechanical strain enhanced proliferation and migration of both estrogen receptor-positive and triple-negative (TNBC) human and mouse BCa cells. They found that exome production by TNBC cells increased upon exposure to oscillatory strain (OS), which correlated with elevated cell proliferation. Increased PD-L1^{+} exome release from BCa cells following OS supported findings demonstrating additive T-cell inhibitory functions in the TME. The authors conclude that mechanical strain within developing BCa tumors promotes invasive and pro-tumorigenic phenotypes, ultimately leading to immunosuppression in the TME by dampening anti-tumor immunity. Investigation into the mechanisms involved could lead to novel therapeutic approaches to target the TME in these instances.

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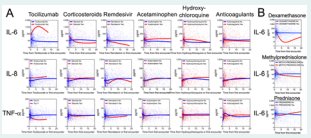
Predictive value of a cytokine signature in COVID-19

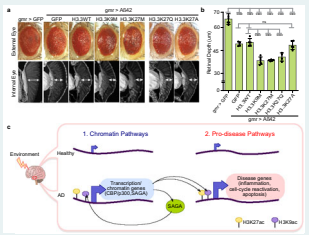
Del Valle et al. investigated predictive biomarkers of infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as COVID-19. In samples from 1484 patients admitted to Mount Sinai Health System in New York, the team assessed serum levels of interleukin (IL)-6, IL-8, tumor necrosis factor-α (TNF-α), and IL-1β and followed the patients for up to 41 days from admission (median, 8 days). On their own, high levels of IL-6, IL-8, and TNF-α at the time of hospitalization were predictors of patient survival. After adjustment for several other factors, including disease severity, hypoxia, and comorbidities, the data showed that IL-6 and TNF-α remained independent and strong predictors of survival. The group propose that these biomarkers be used in the management and treatment of patients with COVID-19 and considered when stratifying prospective clinical trials. A prediction model built on cytokine levels early in disease might inform healthcare allocation and prioritization of individuals at highest risk.



Nature Medicine 2020;26:1636–1643; https://doi.org/10.1038/s41591-020-1051-9

Investigation of epigenomic alterations in Alzheimer's disease

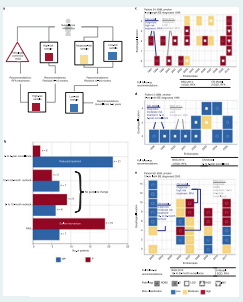
To identify molecular pathways involved in Alzheimer's disease (AD), Nativio et al. integrated transcriptomic, proteomic, and epigenomic analyses of postmortem human brains. They observed upregulation of transcription- and chromatin-related genes, including specific histone acetyltransferases H3K27ac and H3K9ac. The proteomic screen revealed that these enzymes were enriched in AD samples, and epigenomic profiling revealed that gains in their activity were linked to transcription, chromatin, and disease pathways in AD. Overexpression of these genes in a fly model of AD illustrated amyloid-β42-driven neurodegeneration on an increased scale. The data collectively implicates reconfiguration of the epigenome in development of AD, with H3K27ac and H3K9ac dysregulating transcription- and chromatin-gene feedback loops. These results provide novel avenues for investigation not only into the disease's development but potentially into epigenetic strategies for early-stage treatment.



Nature Genetics 2020;52:1024–1035; https://doi.org/10.1038/s41588-020-0696-0

Genomic prediction to stratify therapeutic options in esophageal cancer

Shallow whole-genome sequencing was performed on 777 biopsies collected over 15 years from 88 patients with Barrett's esophagus, a known precursor lesion in the development of esophageal cancer. The authors demonstrated that aneuploidy and driver mutations could be distinguished in the samples to enable progression from stable disease to be determined prior to clinical presentation, and they validated their findings in two independent cohorts. They explain how these low-cost methods can be applied to standard-of-care biopsy samples, leading to earlier treatment for those at high risk and avoiding unnecessary treatment for those who could benefit from surveillance-only options.



Nature Medicine, published online 7 September 2020; https://doi.org/10.1038/s41591-020-1033-y

Emma Judson contributed to these reviews.