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MODERN PATHOLOGY

Holistic assessment of epithelioid hemangioendothelioma

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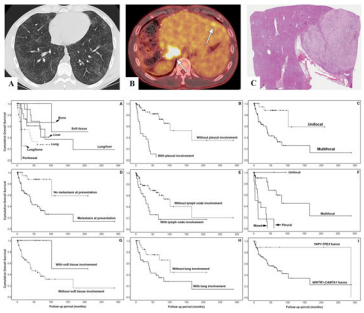

Rosenbaum et al. investigated the pathologic and molecular factors that predict heterogeneity of epithelioid hemangioendothelioma. Two fusions are known predictors. *WWTR1-CAMTA1* is present in classic epithelioid hemangioendothelioma regardless of clinical behavior, while *YAP1-TFE3* fusions have been less thoroughly explored. Within a larger cohort of patients, 18 were isolated from the Memorial Sloan Kettering–IMPACT targeted DNA sequencing clinical sequencing program to identify secondary genetic alterations. More than half showed genetic alteration beyond the characteristic gene fusion. Patients with the classic *WWTR1-CAMTA1* had inferior 5-year overall survival (59%) compared with patients with tumors harboring the less common *YAP1-TFE3* fusion (86%). Laying out the data on Kaplan–Meier plots made it possible to assess survival on more than just this level, taking into account elements such as stage at presentation, soft-tissue involvement, primary site, and lymph node/lung/pleural involvement. These findings contribute to a more integrated profile of the disease that may influence clinical decision-making in the future.

Discrepancies in PD-L1 staining due to tumor heterogeneity

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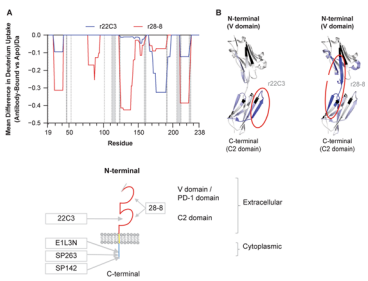

The development and use of independent commercially available programmed cell death ligand-1 (PD-L1) immunohistochemical predictive assays are common in clinical practice. Studies have shown different levels of PD-L1 staining patterns between assays, and there is conjecture as to whether antibody-binding epitopes are responsible. Lawson et al. distinguished the epitopes responsible for antibody binding, using several high-resolution assays of their own, and the results show differences. SP263 and SP142 both bind to an identical epitope in the cytoplasmic domain at the extreme C-terminus of PD-L1, overlapping considerably with that used by E1L3N but distinct from 22C3 and 28-8, which bind to the extracellular domain at different sites. When the group compared all the assays, they found that the staining patterns were not significantly different when staining protocols were altered, despite the evidence of distinct antibody-binding sites. They propose that discrepancies between assays are more likely due to tumor heterogeneity, assay, or platform variables than to antibody epitope.

LABORATORY INVESTIGATION

Maternal diet intervention improves offspring lipid metabolism

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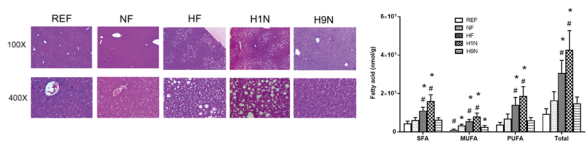

With levels of obesity rising worldwide, Zhou et al. investigated whether maternal diet intervention affected lipid metabolism in offspring. They studies mice fed either a normal-fat diet (NF) or a high-fat diet (HF) for 12 weeks prior to pregnancy, with the HF group divided to transition to an NF diet 1 week (H1N) or 9 weeks (H9N) before pregnancy. When hepatic steatosis, glucose intolerance, hepatic free fatty acid composition, and blood lipid panels were compared, the HF and H1N groups displayed severe deficiencies, and the H9N group was similar to the NF group. The

physiological changes were completely or partially rescued in the H9N offspring. The group concluded that early maternal diet intervention may be effective in reducing the risk of offspring nonalcoholic fatty liver disease (NAFLD) caused by maternal diet, indicating a need to develop diet intervention strategies and education to prevent obesity and NAFLD in mothers and children.

A novel model of mast cell deficiency

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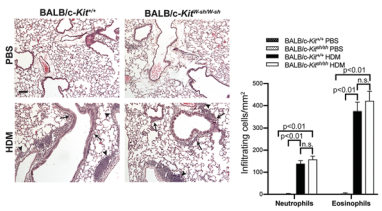

Seeking to better model mast cell involvement in antigen-induced asthma pathology, Hernandez et al. developed an in vivo mast cell–deficient model capable of providing data across genetic backgrounds. Previous models have been restricted to a single genetic background and were often hampered by other phenotypic abnormalities associated with decreased *c-Kit* expression/function. BALB/*c-Kit*$^{W\text{-}sh/W\text{-}sh}$ mice were mast cell–deficient and exhibited splenomegaly with increased splenic hematopoiesis. IgE-dependent passive cutaneous anaphylaxis was absent in these mice, and chronic allergic inflammation of the airways developed. The group proposes that this model, in conjunction with existing models, will support investigation of the roles of mast cells in inflammation and help to identify which of these roles might be influenced by the genetic background of the mouse strain tested.

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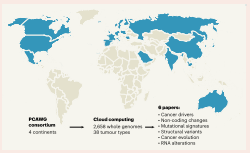
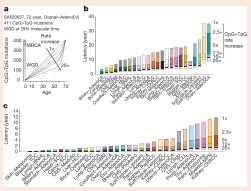
A bold new global approach to cancer genome analysis

The International Cancer Genome Consortium/The Cancer Genome Atlas (ICGC/TCGA) Pan-Cancer Analysis of Whole Genomes (PCAWG) project performed whole-genome sequencing and integrative analysis on more than 2,600 primary cancers (38 tumor types) and their matching normal tissues. This allowed investigation of non-protein-coding genes and assessment of the often ignored 99% of the genome that is noncoding. The project involved an interdisciplinary group of scientists from four continents—comprising a total of 744 institutional affiliations—who overcame major technical, legal, and ethical challenges to carry out distributed analyses while protecting patient data. Researchers were divided into 16 working groups, each focused on distinct facets of cancer genomics, e.g., assessing the recurrence of mutations or inferring tumor evolution.



While it is known that cancer is the second most frequent cause of death worldwide, "cancer" is a term used to denote a set of diseases characterized by autonomous expansion and spread of a somatic clone, with no single cellular program directing any of the behaviors that seem characteristic. The PCAWG collaboration was established as a technical working group to perform informatics analyses by aggregating raw sequencing data from different working groups that studied individual tumor types, aligning the sequences to the human genome and delivering a set of high-quality somatic mutation calls for downstream analysis. The consortium characterized mutational signatures using 84,729,690 somatic mutations from 4645 whole-genome and 19,184 exome sequences that encompass most types of cancer, both common and rare. They identified 49 single-base-substitutions, 11 doublet-base-substitutions, 4 clustered-base substitutions, and 17 small insertion-and-deletion signatures that, combined with epidemiological and other data, can provide more detailed insight into carcinogenesis.

Papers in this collection were organized by focus, structural variation, tumor evolution, mutational signatures, cancer drivers, gene regulation, and the tools developed to perform the analysis. Since 1976, when the concept of a cancer evolutionary process was first presented, the characterization has been in terms of random mutations and natural selection. A cancer cell harboring a mutation that confers high fitness proliferates rapidly, becoming the most prominent cell clone in the population. This phenomenon, called a clonal sweep, occurs in recurring cycles during cancer growth. Cancer evolution is most effectively studied by sequencing multiple regions of a tumor over time, but it can also be reconstructed from a single biopsy—the approach taken by Gerstung et al. in their paper. The PCAWG brought together thousands of scientists, working toward common goals, with limitation only in the lack of clinical data to correlate their findings with patient outcomes and treatments. Adding in these data, along with the broad availability and quality of the data set, will lead to biological insights that will by no means be limited to those published in this collection and will inspire future investigations. The 22 papers currently in this collection published across the Nature journal family, along with insightful commentaries, can be viewed as an open-access special collection at https://www.nature.com/collections/afdejfafdb.



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Emma Judson contributed to these reviews.