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MODERN PATHOLOGY

Molecular testing for fibrolamellar carcinoma

See page 141

DNAJB1-PRKACA gene fusion has been identified in fibrolamellar carcinomas, along with expression of cytokeratin 7 and CD68. Using fluorescence in situ hybridization (FISH) designed to detect this fusion, Graham and colleagues analyzed a pool of 124 cases of previously classified fibrolamellar carcinoma. Of the 124, central review agreed that 104 were typical of fibrolamellar carcinoma; 12 were classified as possible and 8 as unlikely. FISH was positive for *PRKACA* rearrangement in 102 of 103 typical fibrolamellar carcinoma cases, 9 of 12 of the possible cases, and none of 8 unlikely cases. To validate the specificity of diagnostic criteria and FISH, the group evaluated 88 conventional hepatocellular carcinomas; all were negative for rearrangement. The data in this study show that detection of *PRKACA* rearrangement has a sensitivity of 99% for the diagnosis of fibrolamellar carcinoma. Thus, compatible morphology with molecular confirmation and/or use of an immunohistochemical panel that includes CK7 and CD68 constitute a highly effective diagnostic approach.

Anaplastic sarcomas of the kidney

See page 169

First described in 2007, anaplastic sarcoma of the kidney is an exceedingly rare tumor (fewer than 35 cases reported). It is characterized by cysts and solid areas composed of

bundles of undifferentiated spindle cells, cartilage, or chondroid material. Wu *et al* immunohistochemically demonstrated that TP53 was overexpressed in six of nine cases. An eponymous syndrome is identified by germline mutations in *DICER1*, and the authors found a connection between *DICER1* syndrome and anaplastic sarcoma of the kidney. Indeed, eight of nine tumors exhibited the same *DICER1* mutation in the somatic tumor cells, but it was absent in matched normal tissue. Co-occurrence of a *TP53* mutation was shown in three of nine cases. More work will be needed to validate the *DICER1* mutations and to show a predisposition for this tumor in *DICER1* syndrome, but screening for both germline and somatic *DICER1* mutations should be considered in cases of suspected anaplastic sarcoma of the kidney.

LABORATORY INVESTIGATION

Nonlinear microscopy for breast cancer

See page 150

Standard methods for evaluating surgical margins have caused delays and required multiple surgeries within the breast cancer surgical field. Cahill *et al* propose a method for speeding this process and reducing the need for multiple surgeries. They achieved real-time histological evaluation of breast cancer surgical specimens by staining specimens with alternative markers and using fluorescence nonlinear microscopy (NLM). NLM was able to identify crucial features, comparing normal tissue with invasive carcinoma as well as identifying inflammation and fibrous and adipose stroma along with other features. Earlier confirmation of complete resection would reduce the need for repeat surgeries, thereby lowering treatment costs and improving patient

outcomes, in terms of both morbidity and distress.

Maldi imaging in comparative medicine

See page 141

Discrepancies between an animal model and the human disease it is intended to model have complicated research. Aichler *et al* sought to directly compare a mouse model of pulmonary fibrosis with the human form of the disease using microarray and mass-spectrometry techniques. The group identified 1,366 molecules that were common to the human and mouse lesions. By normalizing these molecules by abundance relative to molecular ion peaks in humans, the number was reduced to 900 targets. The 900 molecules were annotated by alignment with the Metlin and KEGG databases and subjected to pathway enrichment, which identified six pathways with the highest enrichment, with metabolism forming the common link between these pathways. While more work needs to be done to validate these comparisons, the authors propose that their protocol can be used to help validate both established and newly engineered animal models.

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Mismatch repair and reduced mutation rates

Historically, although heterogeneity of mutation rates across genomic regions has been shown, the mutation rates between exons and introns are thought to be equivalent. Frigola *et al* found fewer somatic mutations in exons. Historically this discrepancy was thought to be due to negative selection in exons, but the authors found unexpected higher DNA mismatch-repair (MMR) activity in exonic regions. Mutations in exons are thus repaired prior to replication and stable incorporation. Some tumor types, such as colorectal and endometrial tumors, have been shown to acquire microsatellite instability (MSI) when the MMR system is deficient. The group proposes that impaired MMR function (MSI-high) would show a decreased exonic mutation burden compared with POLE mutant or MSS tumors. Formerly established mechanistic links between H3K36me3 and the recognition of mismatches might be explained by the exonic enrichment of this histone mark in cells. This has important implications for research into the development of tumors and evolution of the genome.

Nature Genetics, published online 6 November 2017; doi:10.1038/ng.3991

Statistical pressure in cancer evolution

Gene mutation analysis is common in oncological research, but little effort has been expended on genes whose wild-type sequences are necessary for tumor growth. Given the challenges presented by the heterogeneity of cancer mutation, Weghorn and Sunyaev have developed a hierarchical probabilistic framework that allows modeling of coding point mutations based on the variation in observed mutation rates across the genome. By distinguishing between the positive selection of gene mutations and regulatory elements that drive cancer development, the authors' model could detect the signal of negative selection of these wild-type sequences across several of the 17 cancer types assessed. They propose that the rapid expansion of cancer-sequencing data sets has necessitated the development of hierarchical models such as theirs, which will enhance cancer driver detection by identifying both mutated and wild-type genes that are indispensable to cancer.

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Resistance to targeted therapy

Advances in targeted medicine have revolutionized oncological medicine, leading to the development of drugs designed to influence specific genetic alterations and tumor markers. However, genetically driven resistance to these therapies limits patient survival and is a key area for ongoing research. Blakely *et al* identified co-occurring oncogenic events in advanced-stage EGFR-mutant lung cancers, including new pathways that limit EGFR-inhibitor responses in the clinic. These co-occurring alterations, in *CTNNB1* and *PIK3CA*, exhibit nonredundant functions that cooperatively promote tumor metastasis or limit EGFR-inhibitor response. The current paradigm is to focus on a single oncogenic driver; this work demonstrates the need to take into account the presence and evolution of co-occurring genetic alterations when evaluating responses to targeted therapy in both basic and clinical research.

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