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MODERN PATHOLOGY

Gene alterations in AFX and PDS

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The genomics of atypical fibroxanthoma and pleomorphic dermal sarcoma is poorly understood. Griewank and colleagues subjected several such tumors to targeted next-generation-sequencing approaches and DNA copy-number analysis. A total of 41 atypical fibroxanthomas and 40 pleomorphic dermal sarcomas were assessed—initially using the coding region of 341 oncogenes for a discovery subset and then downselecting to focus on 11 highly mutated genes. The authors found gene alterations in more than half the analyzed samples, including *FAT1*, *NOTCH1/2*, *CDKN2A*, *PT53*, and *TERT* promoter. Overall, the mutational profiles were very similar in both neoplasms, although activating RAS mutations were identified in three pleomorphic dermal sarcomas but not found in atypical fibroxanthoma. Ultraviolet radiation signature mutations were prominent in both tumors. These findings are consistent with these neoplasms representing a spectrum, with depth of invasion being a differentiator between expected outcomes after complete excision. Sample pooling overcomes heterogeneity.

Laser spectroscopy-assisted diagnostic pathology

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The lack of convenient or available techniques has historically made it difficult for pathologists to investigate the sources or effects of disparate exogenous materials in clinical specimens.

Busser *et al* sought to develop a technique using laser-induced breakdown spectroscopy (LIBS). This technique enables visualization of chemical elements such as aluminum, titanium, copper, and tungsten within paraffin-embedded specimens, making the images stackable alongside conventional histology. The LIBS system takes 3 hours to scan a 6-cm² surface with 10-Hz-frequency lasers or 20 min with 100-Hz lasers. Combining the information from LIBS, histopathological analysis, and pathologists' experience, the group was able to assess immune reactions to aluminum salts, metal particles left behind from surgical instruments or implants, and biocompatibility of prosthetic devices such as pacemakers, ear piercings, and even tattoo inks. This new approach provides a promising avenue for screening for foreign embedded substances. Immunological landscape of breast cancer

LABORATORY INVESTIGATION

Detecting gene translocations in lung adenocarcinoma

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Current immunohistochemistry and fluorescence in situ hybridization techniques for detecting *ALK*, *ROS1*, and *RET* rearrangements in lung adenocarcinoma can be difficult to interpret and expensive.

Using probes and ligation-dependent reverse-transcription polymerase chain reaction (LD-RT-PCR) to detect gene rearrangements costs less and can provide results in 2 days. Piton *et al* developed a

multiprobe LD-RT-PCR kit that specifically targets mutations commonly found in lung adenocarcinomas. In a direct comparison of the two techniques, the group was able to show correlative results, with some gaps. There were cases in which LD-RT-PCR did not provide positive results, possibly indicating that some partner genes were not in the panel designed for the assay and thus could not be detected. Newly identified partner genes and breakpoints will require regular update of the probes. Because the reaction itself can accommodate as many as 150 probes, the technique allows flexibility of design.

Microscale characterization of prostate biopsies

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Yuting *et al* investigated an optical method to distinguish with high diagnostic accuracy between benign prostate tissue and cancerous tissue, as well as to determine the Gleason grade of the latter. Using a large set of biopsy tissues, obtained from men suspected to have prostate cancer, the group compared two techniques: optical coherence elastography (OCE) and second-harmonic-generation (SHG) imaging. The two techniques look for different features of the tissue structure—OCE assesses tissue stiffness and SHG identifies the orientation of collagen structure. Tissue stiffness was higher in cancerous tissue. Collagen fibers tended to form in a reticular pattern in cancerous lesions as opposed to a papillary pattern in benign tissue. Together, the two techniques constitute the basis of a new biomechanical assay for combining markers that has the potential to identify cancer and correlates with Gleason grading. Application to other diagnostic settings is also of interest.

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Gene fusions in cancer metabolism

In-frame oncogenic gene fusions such as *FGFR3-TACC3* (F3-T3), identified in human glioblastomas, have been shown across multiple tumor types. While these fusions are known to be potent oncogenes and potential targets of therapeutic interventions, there is still much to learn about the downstream oncogenic signaling pathways. Human tumors with *FGFR3-TACC3* can be characterized by the activation of mitochondrial functions, with activation of oxidative phosphorylation and mitochondrial biogenesis. Phosphorylation of the phosphopeptide PIN4 forms an intermediate step in mitochondrial metabolism, and this pathway triggers biogenesis of peroxisomes and the synthesis of new proteins. Phospho-PIN4 (Y122)-positive cytoplasmic structures in *FGFR3-TACC3* astrocytes colocalized with PMP70, indicating a role in trafficking new peroxisomal membranes. Coordinated activation of these anabolic pathways leads to accumulation of reactive oxygen species and increases in mitochondrial metabolism. These findings regarding inhibition of oxidative phosphorylation in glioblastoma patients with *FGFR3-TACC3* should be explored.

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SELENBP1 in extraoral halitosis

Pol *et al* looked into a process involving SELENBP1 that was not previously known to exist in humans. The group identified SELENBP1 mutations in five patients with cabbage-like breath odor, attributable to high levels of methanethiol and dimethyl sulfide. Biallelic pathogenic SELENBP1 mutations were identified in 1:90,000, corresponding to a carrier

frequency of 1/300 individuals, whereas the frequency of extraoral halitosis has previously been estimated to be 0.25–1.5%, indicating that SELENBP1 may explain only a minority of these cases. When assessing the low SELENBP1 expression in patient fibroblasts, the group found that introducing exogenous SELENBP1 in these cells increased methanethiol oxidase activity. The authors propose that SELENBP1 controls the levels of methanethiol concentration, crucial for keeping methanethiol concentrations in the body below the odor threshold. Further research into the role of SELENBP1 in extraoral halitosis may lead to additional methods for resolution.

Nature Genetics 2018;50:120–129; doi:10.1038/s41588-017-0006-7

New targets in treating obesity

Previous genome-wide association studies (GWAS) have identified more than 250 loci for body mass index, although many are polymorphisms in noncoding regions. Neuronal pathways are commonly implicated. In a large GWAS, Turcot *et al* identified 14 coding variants in 13 genes. Eight of the variants were in genes newly implicated in human obesity, two were in genes previously observed as mutated in extreme obesity, and two were in *GIPR*. *Gipr*-deficient mice have been shown to be protected from diet-induced obesity and their metabolic rate is higher than that in wild type. *GAPGEF3* shows complex effects on adipocyte biology, energy, and glucose metabolism in animal models. The gene-set-enrichment techniques support a role for nonneuronal mechanisms, given that *CIDEA* and *ADH1B* are linked to insulin action and adipocyte biology. Individual genes influence obesity and might provide potential treatment targets.

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