Modern Pathology (2018) 31, 1488–1489

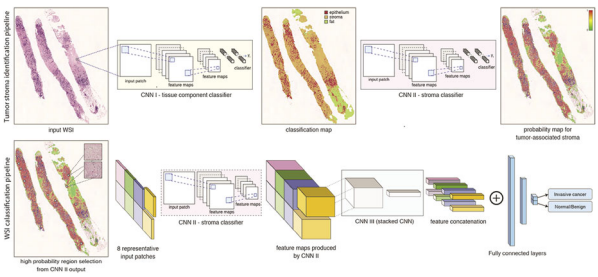
INSIDE THE USCAP JOURNALS

doi:10.1038/s41379-018-0135-2

MODERN PATHOLOGY

Algorithm to analyze stromal features of breast cancer

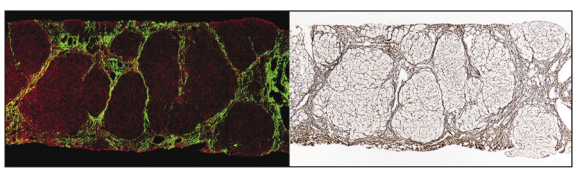
doi:10.1038/s41379-018-0073-z



Stromal changes in the breast microenvironment are key in the development, growth, and metastases of breast cancer; however, the subjective nature of pathologists' assessments of these features limits diagnostic utility. Bejnordi et al. used an automated machine-learning technique to analyze 2387 stained tissue sections of benign and malignant biopsies from 882 patients aged 40–65 years. They trained an algorithm to discriminate between stroma surrounding invasive cancer and stroma from benign biopsies using deep convolutional neural networks. The algorithm was able to distinguish biopsies diagnosed as invasive cancer from benign biopsies based solely on stromal characteristics and even to detect tumor-associated stroma in grade 3 versus grade 1 ductal carcinoma. The group propose that these algorithms could enhance the classification of biopsies and be used in further investigation into underlying biology of breast cancer.

Quantifiable imaging technique for assessment of fibrosis regression

doi:10.1038/s41379-018-0059-x

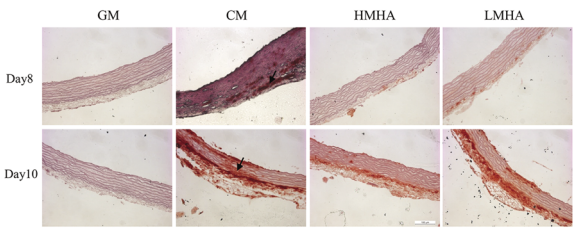


Paired biopsy samples from chronic hepatitis B patients were imaged with fully automated second-harmonic-generation/two-photon fluorescence-based microscopy, to investigate fibrosis reversal following antiviral therapy. The technique provides a stain-free, quantitative method for assessing tissue samples. Ishak stage and qFibrosis score showed four types of response to 78 weeks of therapy—fast reverse (9%), reverse (63%), stable (15%), and progress (13%)—with collagen feature changes predominantly in the septal and fibrillar areas. Average width, maximum width, number of fibers, and number of cross-link fibers were parameters that correlated with fibrosis reversion in 1060 septa analyzed by septal width (30 μM between progressive and regressive septa), which proved to be the most predictive indicator of prognosis. Further analysis of samples as the patients in the study progress through treatment, along with increased sample size, will refine the data quality.

LABORATORY INVESTIGATION

Vascular calcification influenced by hyaluronan-BMP2 signaling

doi:10.1038/s41374-018-0076-x

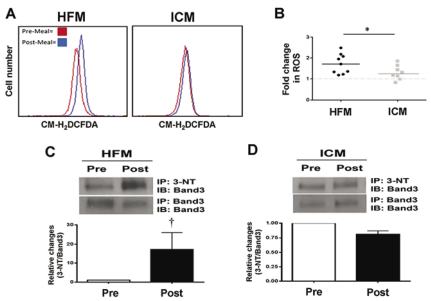


Kong et al. sought to investigate the possible role of hyaluronan, known to inhibit osteoblast differentiation in cartilage, in vascular calcification using both in vitro and ex vivo models. In rat models they found that hyaluronan treatment reduced calcification of vascular smooth muscle cells in a dose-dependent manner, decreasing expression of alkaline phosphatase and bone-related molecules Runx2, BMP2, and Msx2. The reverse was also true—that inhibition of hyaluronan synthesis promoted calcification. Specifically, BMP2 signaling was inhibited following hyaluronan treatment. A role of extracellular matrix, and therefore hyaluronan, in vascular calcification was already known. However, previous studies had focused on other components of the extracellular matrix, and the specific role of hyaluronan on mineral deposition was a motivator for the current study. The data indicate a new avenue of research into

hyaluronan as a potential therapeutic target for prevention and treatment of vascular calcification.

Effects of high-fat meal consumption in patients with atherosclerosis

doi:10.1038/s41374-018-0038-3

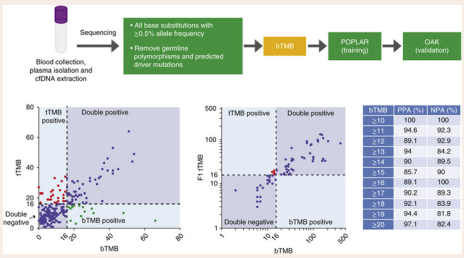


The downstream effects of high-fat meal consumption have largely been established, but the mechanisms are not yet fully understood. Benson et al. had previously reported the effect of high-fat consumption on erythrocyte remodeling in mice. In the current study, they investigated the interaction between erythrocytes, inflammatory cells, and blood vessels, as well as the role of erythrocytes in vascular function, in human subjects. Following a high-fat meal, levels of free fatty acid, triglycerides, and cholesterol were elevated and flow-mediated dilation of blood vessels was impaired; in addition, blood smears revealed breakdown and remodeling of blood cells. The findings demonstrate that a single high-fat meal in humans induces pathological erythrocyte remodeling with elevated myeloperoxidase levels, possibly resulting in oxidative stress and the destabilization of plaques within the vessels, with implications for elevated risk in patients with atherosclerosis.

nature.com/pathology

Blood-based biomarker of tumor mutational burden

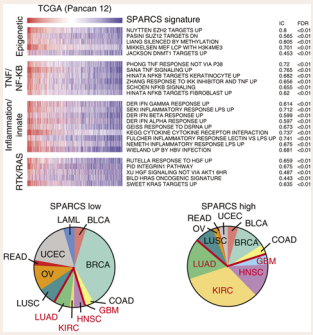
Levels of programmed death-ligand 1 (PD-L1) expression, along with tumor mutational burden, are used in non–small cell lung cancer (NSCLC) to assess programmed death 1/PD-L1 inhibition. Because acquiring sufficient tissue for the testing is not always easy, a noninvasive assay to identify these patients would be valuable. Gandara et al. have developed a blood-based assay to measure tumor mutational burden in plasma (bTMB) that reproducibly identifies patients with clinical benefit from atezolizumab treatment. The assay uses hybridization capture to target 1.1 Mb of genomic coding DNA. Immunohistochemistry showed that bTMB is independent of high tumor PD-L1 expression. The data indicated that bTMB with a cut point ≥16 reproducibly identified patients who benefited from atezolizumab in two independent patient cohorts. bTMB could thus serve as a predictive biomarker in treatment decision making for NSCLC patients.



Nature Medicine, published online 6 August 2018; doi:10.1038/ s41591-018-0134-3

Innate immunity could be influencing immunotherapeutic efficacy

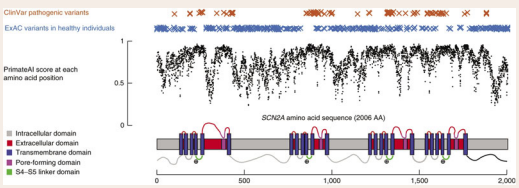
Chemorefractory small-cell lung cancer and resistance to targeted therapeutics are potentially influenced by cytokines secreted from mesenchymal tumor subpopulations. Cañadas et al. identified a subclass of endogenous retroviruses that engage immune signaling through stimulated 3′ antisense retroviral coding sequences regulated by STAT1 and EZH2. They showed that de-repression results in double-stranded RNA generation resulting from bidirectional transcription from STAT1-activated gene promoter and the 5′ long terminal repeat of the antisense endogenous retrovirus. Mesenchymal tumor subpopulations with high AXL/MET expression and low EZH2 levels trigger expression of a specific set of endogenous retroviruses when exposed to interferon-γ. The group note that their data suggest that a subclass of endogenous retroviruses, when suppressed, trigger a pathologically innate immune signaling process in cancer and that this needs to be further investigated as it relates to cancer immunotherapeutics such as programmed death-1 blockade.



Nature Medicine 2018;24:1143–1150; doi:10.1038/s41591-018-0116-5

Using deep neural networks to predict clinical impact of mutations

Discerning biological and clinical implications of alterations in human genomes and exomes has been limited by the challenge of distinguishing between genetic variation and disease-causing mutation. Sundaram et al. used the process of elimination to make that distinction in several primate species. They found that common missense variants in primates were largely clinically benign in humans. Using population sequencing of six nonhuman primate species, the group trained a deep neural network to identify pathogenic mutations in rare-disease patients, enabling discovery of 14 new candidate genes in intellectual disability at genome-wide significance by. For example, the deep-learning network assigns high pathogenicity scores to residues at critical protein functional domains of the voltage-gated sodium channel SCN2A, which has implications in epilepsy, autism, and intellectual disability. The investigators see their work as being influential in the campaign to preserve these nonhuman primate species since their preservation might influence our own.



Nature Genetics 2018;50:1161–1170; doi:10.1038/s41588-018-0167-z