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INSIDE THE USCAP JOURNALS

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MODERN PATHOLOGY

Genomic profiling of secretory carcinoma

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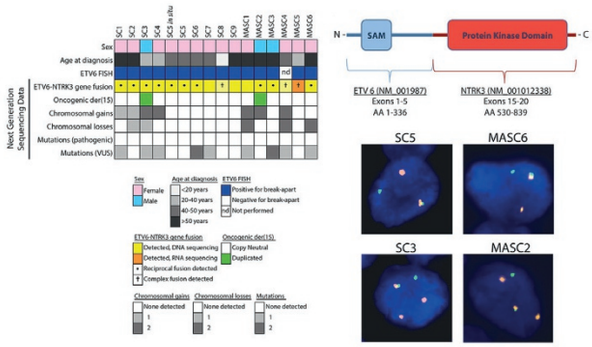

Krings *et al* used next-generation sequencing to analyze a gene panel in secretory carcinomas of the breast and compared them with mammary analog secretory carcinomas of the salivary gland. The cancers share a similar immunophenotype of MUC4, SOX10, and CK5/6 and are primarily triple-negative (or weakly estrogen receptor–positive). While breast secretory carcinoma has a basal-type triple-negative morphologic and immunohistochemical profile, it is more similar to mammary analog secretory carcinomas of the salivary gland than it is to other primary breast cancers. *ETV6–NTRK3* gene fusions define both of these tumor types and are often the single detected genetic aberration. The very low mutation burden of secretory carcinomas make them distinctly different from most basal-type breast carcinomas. The link between breast secretory carcinomas and salivary gland carcinomas is stronger than that between these and other breast carcinomas, indicating that the characteristics of these translocation-driven tumors are genomically driven and site-independent.

Lynch syndrome and colorectal tumorigenesis

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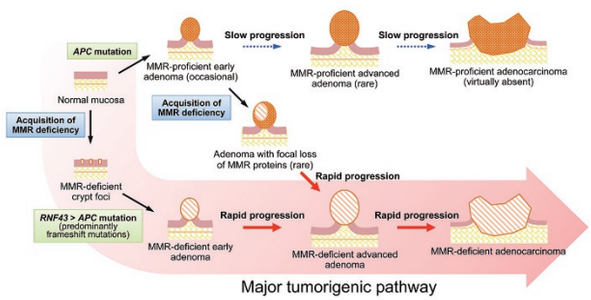

Lynch syndrome, one of the most common inherited cancer-predisposition syndromes, is caused by mismatch repair (MMR) genes. In immunohistochemical analysis, Sekine *et al* found that 68 of 86 adenomas and all adenocarcinomas from patients with Lynch syndrome were deficient for at least one MMR protein and were therefore deemed MMR-deficient. Next-generation sequencing showed that Lynch syndrome–associated colorectal adenomas had different genetic profiles depending on MMR status, with *APC* or *CTNNB1* mutations. Mutation profiles of MMR-proficient adenomas, on the other hand, were indistinguishable from those of sporadic adenomas. The authors propose that WNT pathway activation sufficiently drives colorectal adenoma formation. They showed distinct WNT pathway mutation profiles of Lynch syndrome–associated adenomas and note that MMR deficiency commonly precedes adenoma formation.

LABORATORY INVESTIGATION

NLRP3 in HHcy-aggravated atherosclerosis

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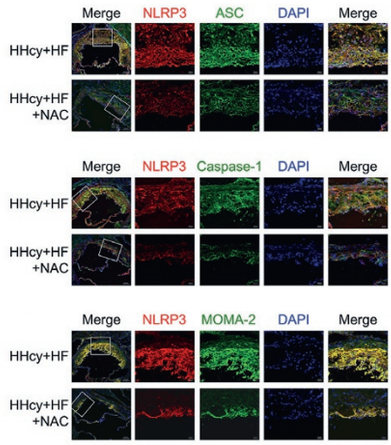

Wang *et al* designed a study to investigate whether the activation of NLRP3 inflammasomes contributes to hyperhomocysteinemia (HHcy)-induced inflammation and atherosclerosis. HHcy was induced in ApoE$^{-/-}$ mice, and an NLRP3 short hairpin RNA viral suspension was injected to knock down the gene. This resulted in increased plasma levels of interleukin (IL)-1β and IL-18, which aggravated macrophage infiltration into atherosclerotic lesions associated with NLRP3 inflammasomes. The group showed that homocysteine-induced NLRP3 inflammasome activation was abolished by *N*-acetyl-L-cysteine. The reactive oxygen species pathway was identified as an activating influence on the HHcy NLRP3 inflammasomes.

The authors demonstrated that activation of NLRP3 inflammasomes has an essential role in HHcy-aggravated atherosclerosis, indicating a promising therapeutic target for intervention in HHcy-associated cardiovascular diseases.

Microfluidics for rapid immunohistochemical analysis of frozen sections

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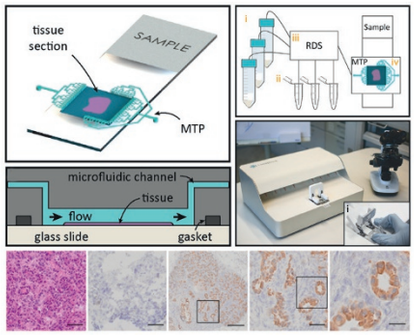

Brajkovic *et al* investigated microfluidic device technologies designed to improve the performance of immunohistochemical assays. The group sought to optimize a complete pan-cytokeratin chromogenic immunostaining protocol for frozen sections using a microfluidic tissue processor. The optimization of the initial tissue preparation came down from 55 minutes to ~8 minutes, from sectioning through drying and fixation, a second drying step, and rehydration. A prototype machine was designed for the experiments that were constrained by typical intraoperative laboratories, and the timing was optimized with the need for rapid pathological examination during surgery. After optimizing the speed of the tests, the authors worked on reproducibility, but a prospective study with higher numbers of samples will be required to fully validate the protocol. Their goal is to provide surgical pathologists with a microfluidics frozen-section immunohistochemistry protocol that will expand what can be achieved rapidly with interoperative frozen sections.

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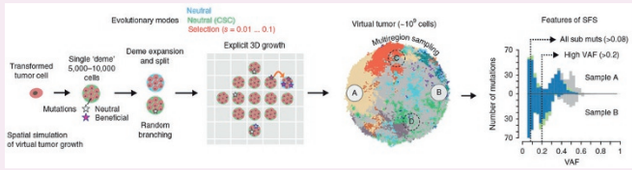
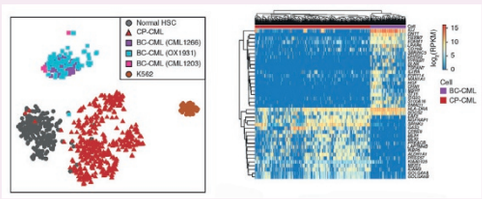
Understanding tumor evolution



The development of precision medicine as a driver for oncological treatment has necessitated a better understanding of tumor dynamics. Sun *et al* used virtual tumors, simulated under different circumstances, to study the tumors' variable clone maps. They found that colorectal tumors exhibit patterns of between-region genetic divergence consistent with effectively neutral growth. A 'true' clone should form a cluster that persists, illustrated by a region where mutations remain grouped. The authors thus developed a classification framework based on capture of between-region subclonal divergence and identified different modes of evolution within and between solid tumor types. An improved ability to discriminate between modes of evolution within tumors will enhance treatment development. Further analysis of passenger alterations, clonal cooperation, and tumor dynamics will advance our understanding of selection in human tumors and its implications for precision cancer treatment.

Nature Genetics, published online 5 June 2017; doi:10.1038/ng.3891

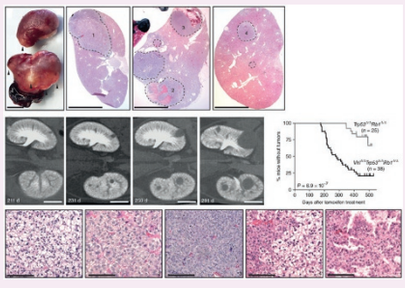
Molecular stem cell signatures in CML



Giustacchini *et al* sought to unravel intratumoral heterogeneity and selective resistance of cancer stem cell (CSC) subpopulations to molecularly targeted cancer therapeutics. They developed a method combining high-sensitivity mutation detection with whole-transcriptome analysis of the same single cell to analyze more than 2,000 SCs from patients with chronic myeloid leukemia (CML). They identified a subgroup of CML SCs with a distinct molecular signature that selectively persisted during prolonged therapy. Using *BCR-ABL* as a marker and a test for various methods of single-cell RNA sequencing, they found that existing methods lacked sufficient sensitivity for mutation detection. Having developed a methodology for single-cell RNA sequencing, they demonstrated that sequencing of SCs at diagnosis as well as during blast crisis in CML patients predicts molecular response to tyrosine kinase inhibitors. Their technique can be applied to assess heterogeneity in clonal CSCs. Although technical challenges remain, the authors are confident that a clinical application is forthcoming.

Nature Medicine 2017;23:692–702; doi:10.1038/nm.4336

Common derivation of human and mouse ccRCC



Clear-cell renal cell carcinomas (ccRCCs) frequently exhibit inactivation of the von Hippel–Lindau tumor suppressor gene (*VHL*), along with copy-number alterations in cell cycle progression genes. Harlander *et al* report that modeling these alterations (*Vhl*, *Trp53*, *Rb1*) renal epithelial cells in mice caused ccRCC, with tumors arising from proximal tubule epithelial cells. Because mouse and human ccRCCs show common recurrent gene mutations affecting the primary cilium, the authors proceeded with their investigations in mouse tumors. Inhibition of hypoxia-inducible factor (HIF)-α transcription factors with acriflavine had therapeutic effects in some tumors, indicating that further investigation is required to assess HIF-α inhibition in ccRCC treatment. The mouse model of $Vhl^{\Delta\Delta}Trp53^{\Delta\Delta}Rb1^{\Delta\Delta}$ provides a tool for investigating ccRCC development and treatment by identifying biomarkers associated with therapeutic sensitivity or resistance.

Nature Medicine, published online 29 May 2017; doi:10.1038/nm.4343

Emma Judson contributed to these reviews.