Modern Pathology (2016) 29, 1290–1291

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doi:10.1038/modpathol.2016.183

MODERN PATHOLOGY

Undifferentiated endometrial carcinomas

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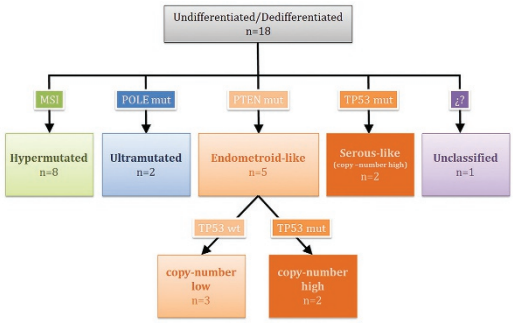

By distinguishing the background molecular genetic alterations of undifferentiated endometrial carcinomas, Rosa-Rosa *et al* aimed to gain insight into the pathogenesis of these uncommon and highly aggressive tumors. Nearly half of the undifferentiated carcinomas in the test group were found to be hypermutated, with mismatch repair deficiency, in contrast to the 15–30% of microsatellite instability in sporadic endometrial cancer. The authors hypothesized that this suggests an intrinsic potential for tumor progression in this group. Two of the undifferentiated carcinomas carried *POLE* mutations leading to ultramutation, which is associated with high-histological-grade carcinomas and morphological heterogeneity. Of the lower-level copy-number-altered endometrial carcinomas, the most frequent driver alteration was *PTEN* mutation, often in combination with mutations in *PIK3CA* and *PIK3R1*. Seventy percent of the assessed tumors showed loss of ARID1A. The group believes that their data capture a more complete picture of the variety of pathways that can result in undifferentiated endometrial carcinomas.

High fidelity of driver chromosomal alterations

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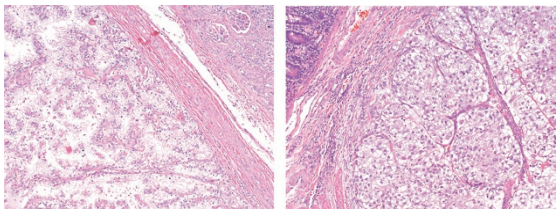

Kouba *et al* investigated mutational diversity in primary and renal cell carcinoma (RCC) and propose that their findings will support the development and implementation of targeted molecular therapies. Clear-cell RCC and papillary RCC tumors were evaluated for chromosome 3p deletion and trisomies 7 and 17, and chromophobe RCC tumors were evaluated for genetic alterations in chromosomes 1, 2, 6, and 10. Of the primary clear-cell RCC tumors, 18% showed deletion of chromosome 3p and were disomic for chromosomes 7 and 17. Of the 16 papillary RCC tumors, 10 showed trisomy for both chromosomes 7 and 17 without 3p deletion. Because the small number of subjects raises the potential for selection bias in the data, confirmation in a larger sample size is needed. The study demonstrates extensive genomic fidelity between primary and metastatic tumors, provides insight into clonal evolution, and has implications for selection of appropriate sources of material for clinical genomic testing.

LABORATORY INVESTIGATION

Vasopressin in polycystic liver disease

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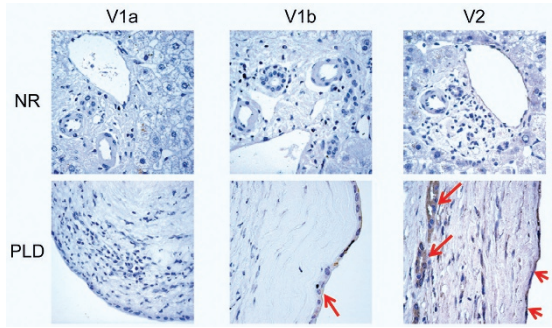

Mancinelli *et al* investigated the three distinct receptor subtypes of neurohypophysial hormone arginine vasopressin (AVP): V1a, V1b, and V2. Cholangiocytes are the target cells in several animal models of cholestasis, including bile duct ligation (BDL) and polycystic liver disease (PLD). Mouse, rat, and human cholangiocytes express V2 receptors that are upregulated following BDL as well as in cholangiocytes lining the liver cysts in patients with autosomal-dominant polycystic kidney disease (PKD). *In vitro* vasopressin administration increased proliferation and cAMP levels of cholangiocytes, a model that represents the immature biliary compartment activated to compensate for cholangiocyte damage. AVP is proposed as a modulator of cholangiocyte proliferation, in which cells are persistently stimulated to proliferate and secrete. This

effect is thought to be enhanced by renal and hepatic concentrating defects and by the increased circulating levels of AVP that occur in both PKD and PLD. This insight could aid management of these diseases based on modulation of the V2 receptor.

miR-139-5p and clinical progression of PBC

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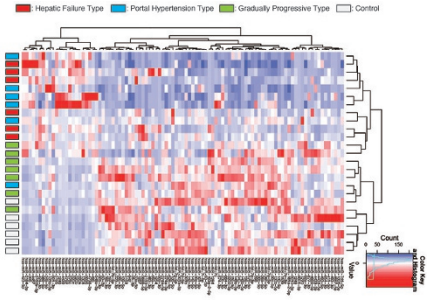

Destruction of intrahepatic bile ducts characterizes primary biliary cholangitis (PBC). Katsumi *et al* evaluated microRNA (miRNA) expression patterns among the PBC subtypes using comprehensive deep sequencing. Using laser-capture microdissection, they histologically identified miRNAs involved in the clinical progression of PBC. Quantitative reverse-transcription PCR showed that miR-139-5p was significantly downregulated in clinically advanced PBC. Examination of uninvolved liver tissue demonstrated that the expression of lymphocyte-derived miR-139-5p was higher than that in hepatocytes, which they postulated could be an indicator of progression and aggravation of PBC. The group identified c-FOS as a target gene of miR-139-5p *in silico*. c-FOS protein functions to suppress inflammatory responses by acting directly on the nuclear factor–κB p65 subunit. The authors propose that miR-139-5p is a novel regulatory factor in PBC progression.

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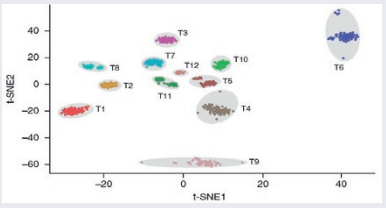
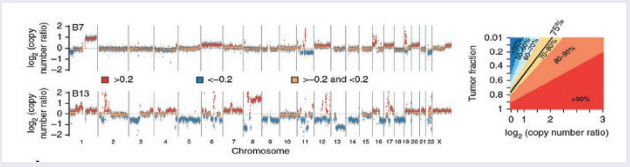
Rapid evolution in breast cancer



Gao *et al* explored the complex genomic rearrangements that evolve during tumorigenesis and aneuploidy in breast cancer. In their model, copy-number alterations (CNAs) are acquired in short bursts of crisis, followed by stable clonal expansions that form a tumor mass. Punctuated copy-number evolution (PCNE) was assessed through highly multiplexed single-cell copy-number profiling to sequence 1,000 cells from tumors in 12 patients with triple-negative breast cancer (TNBC). The group did not detect any intermediate copy-number profiles that would have been indicative of gradual evolution as the tumor cells evolved from diploid to aneuploid genomes. Their data supported the hypothesis that individual tumor cells may be intrinsically programmed to become invasive, metastatic, or resistant to chemotherapy at the earliest stages of tumor growth. Preliminary data in other tumors (colon, prostate, liver, and lung) suggested that PCNE may not be restricted to breast cancer and point to explosive cancer dynamics.

Nature Genetics, published online 15 August 2016; doi:10.1038/ng.3641

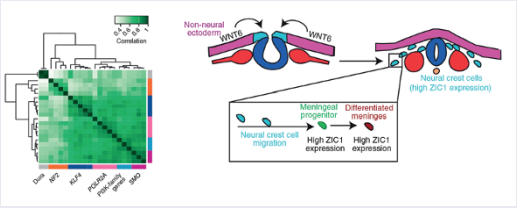
Inferred gene expression from plasma DNA



Nucleosome-protected DNA gets shed into the bloodstream by cells undergoing apoptosis and is broadly described as cell-free DNA (cfDNA). Using whole-genome sequencing of plasma DNA, Ulz *et al* identified two discrete regions of transcription start sites (TSSs). There were supporting data to distinguish patterns of read depth when comparing healthy donors with patients who had metastatic disease. The authors looked at expression of *FGFR1* and *ERBB2* isoforms and calculated the differences in the inferred gene expression in blood from patients with cancer versus healthy donors. The results demonstrated that a particular *ERBB2* isoform was more highly expressed in tumors than in healthy controls. The authors were able to identify the most highly expressed isoform for seven of the eight genes that showed focal amplifications with several TSSs. These data provide a novel view of the genomes of cells that release their DNA into the circulation and expand on existing options for cfDNA analyses.

Nature Genetics, published online 29 August 2016; doi:10.1038/ng.3648

Recurrent *POLR2A* mutations in a meningioma subset



Clark *et al* looked into genomic mutations in RNA polymerase II (*POLR2A*), which mediates the transcription of protein-coding genes. Using next-generation genomic analyses of 775 meningiomas, the group showed recurrent somatic p.Gln403Lys or p.Leu438_His439del mutations in *POLR2A*. Expression profiling across a large cohort of meningiomas identified distinct clusters that were almost completely consistent with established subgroups, suggesting that the transcriptional architecture of each tumor was driven largely by the underlying driver mutation, with differential expression of WNT pathway constituents. Transcriptional machinery could drive tumorigenesis and define mutually exclusive meningioma subgroups. In the *NF2/SARCB1* mutant subgroup, the *BCL2* oncogene and the developmentally important WNT-signaling regulators *DAAM2*, *NKD1*, *FZD4*, and *SFRP2* were expressed in significantly higher amounts. This study enhances our understanding of the factors driving meningioma tumor development and progression and highlights the genomic diversity of this tumor family.

Nature Genetics, published online 22 August 2016; doi:10.1038/ng.3651

Emma Judson contributed to these reviews.