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# INSIDE THE USCAP JOURNALS

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## MODERN PATHOLOGY

### *TERT* mutations in adult granulosa cell tumors of the ovary

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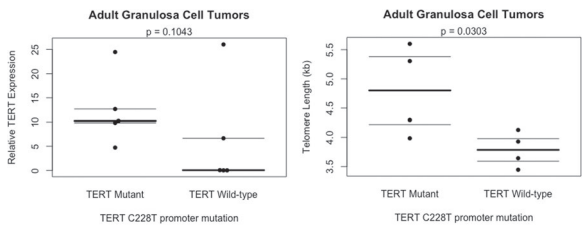
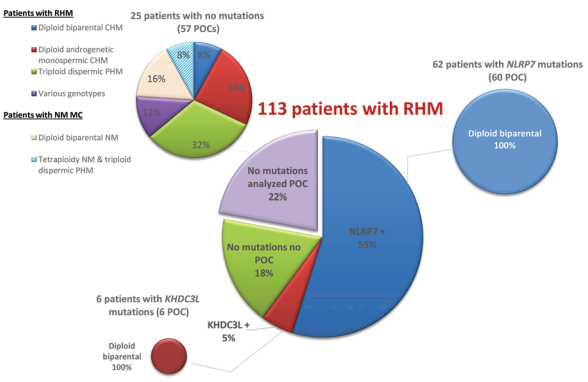



Cancer cells can attain immortality by activating telomerase reverse transcriptase (TERT) to maintain telomere length. Two somatic mutations in the *TERT* promoter (C228T and C250T) have been identified as specific gain-of-function mutations that promote transcriptional activation of *TERT* in several cancers, including ovarian clear-cell carcinomas. To determine the frequency of these mutations in sex cord-stromal tumors, Pilsworth et al. performed whole-genome sequencing on adult granulosa cell tumors and identified a *TERT* C228T promoter mutation in 50% of tumors. Adult granulosa cell tumors with mutated *TERT* promoters showed increased expression of *TERT* messenger RNA and exhibited significantly longer telomeres compared to tumors with wild-type *TERT* promoters. Additionally, patients with mutated *TERT* promoters had a lower survival rate. Telomere biology may be an important parameter in the progression of adult granulosa cell tumors.

### The genetics of recurrent hydatidiform moles: new insights

doi:10.1038/s41379-018-0031-9

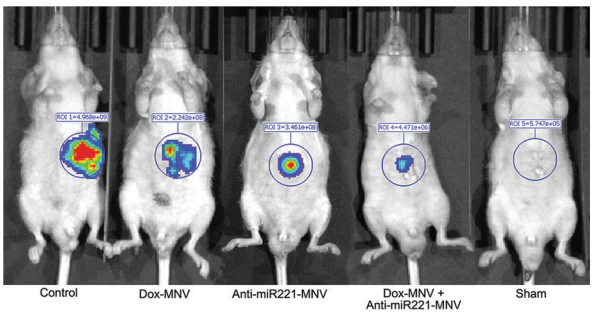



Hydatidiform mole is an aberrant human pregnancy characterized by early embryonic arrest and excessive trophoblastic proliferation. Among patients with recurrent hydatidiform moles, 50–80% have biallelic pathogenic variants in the imprinting genes *NLRP7* or *KHDC3L*. In the remaining patients, the genotypic types of the moles are unknown. Nguyen et al. characterized hydatidiform mole tissue from patients with and without *NLRP7* or *KHDC3L* mutations. They found that all hydatidiform moles from patients with biallelic *NLRP7* or *KHDC3L* mutations were diploid biparental, but those from patients without mutations were heterogeneous: 8% diploid biparental, 24% diploid androgenetic monospermic, and 32% triploid dispermic. The authors conclude that patients with no recessive mutations in the known genes are different from those with mutations, exhibiting as-yet-unknown mechanisms for the origin of their hydatidiform moles.

## LABORATORY INVESTIGATION

### Milk nanovesicles for drug delivery

doi:10.1038/s41374-018-0053-4



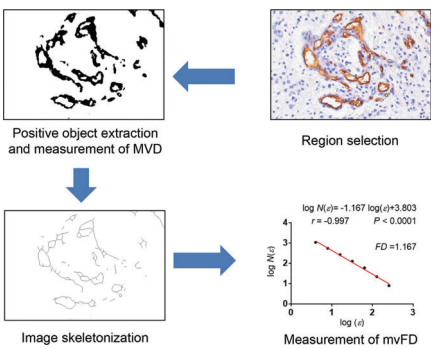

Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality worldwide. Because HCC is largely resistant to chemotherapy, an ideal drug delivery method would selectively target tumor cells within the liver while enabling coadministration of both RNA-targeting and anticancer therapies. Accordingly, George et al. evaluated the efficacy of milk-derived nanovesicles (MNVs) for the delivery of anticancer agents into intrahepatic tumors. They prepared MNVs loaded with the chemotherapeutic agent doxorubicin (dox-MNV), and, because miR-221 is associated with development of orthotopic intrahepatic HCC, a second set of vesicles was filled with miR221 antisense oligonucleotides (anti-miR221-MNV). The efficacy of dox-MNV and anti-miR221-MNV in arresting tumor growth was then assessed in intrahepatic tumors induced in nude mice. The authors found

that combination treatment of intrahepatic tumors using both agents resulted in a marked reduction of tumor size and an increased survival rate, suggesting a need for further studies.

## Microvascular fractal dimensions and glioblastoma

doi:10.1038/s41374-018-0055-2

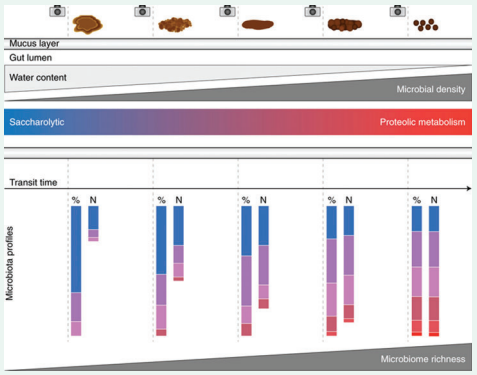
Although their microvascular profile is included in World Health Organization (WHO) glioma grading criteria, evaluating microvessels in WHO grade IV glioblastoma (GBM) is particularly difficult because the vessels exhibit heterogeneous morphology. To address this problem, Chen et al. employed a new parameter—microvascular fractal dimension (mvFD)—to quantify microvessel complexity. They also developed software to automatically identify mvFD from microvessel-stained immunohistochemical images of GBM. The authors found that mvFD effectively quantified the morphological complexity of GBM microvasculature. Furthermore, high mvFD values favored survival of GBM patients and predicted a better response to chemotherapy. In addition, mvFD was inversely correlated with microvasculature-normalized tumor cell proliferation and glycolysis. These findings highlight the potential diagnostic and prognostic utility of mvFD in glioma patients.




# nature.com/pathology

### Rethinking the gut microbiome

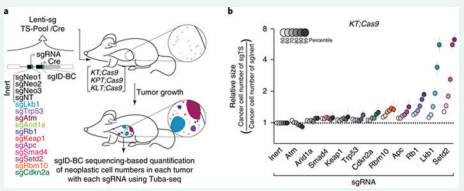
Estimates suggest that there are as many as three times more bacterial cells (the microbiome) than human cells in our body and that the bacterial genes we carry outnumber our human genes by about 100 to 1. The National Institutes of Health–sponsored Human Microbiome Project has mapped the microbiome of oral, nasal, skin, gastrointestinal, urogenital, and other sites in 300 healthy adults. This effort and many others are now correlating properties of the microbiome with a variety of disease states, from inflammatory bowel disease to cancer, although establishing causality has been a recurrent challenge. In general, richness or diversity of the microbiome, particularly in the gut, has been associated with health. In their Comment, Falony et al. argue that, from an ecological standpoint, richness might represent a stage of development reflected by habits and the disease state rather than a marker of community resilience—further complicating epidemiological studies and causal hypotheses.




*Nature Microbiology* 2018;3:526–528; doi:10.1038/s41564-018-0143-5

### Modeling the fitness landscape in lung cancer

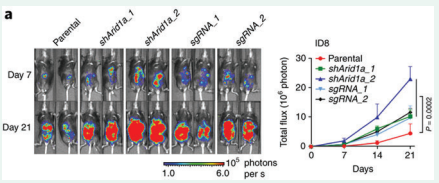
While we are currently adept at cataloging the mutations present in cancer, we know little of the functional effects of single genes or specific combinations in cancer. In a study reported in *Nature Genetics*, Rogers et al. used CRISPR/Cas9-mediated gene editing with barcoding and ultra-deep sequencing to examine the effects of particular combinations of gene mutations in a mouse model of lung cancer. Interestingly, they found that the majority of genes they studied are context-dependent and that their ability to drive growth is specifically dependent on the presence or absence of functional *Trp53* or *Lkb1*. Most genes studied appeared to be adaptive only within specific tumor genomic contexts. The authors conclude that analysis of larger mouse cohorts is needed to enhance the ability to identify genetic interactions and that use of their context-constrained models and fitness approach would help us better understand how cancer drug selection pressure determines mutational fitness in certain genomic contexts.




*Nature Genetics* 2018;50:483–486; doi:10.1038/s41588-018-0083-2

### *ARID1A* and the cancer mutator phenotype

*ARID1A* is one of the most commonly mutated tumor suppressor genes in cancer. Because *ARID1A* mutations usually lead to loss of protein expression, it is a poor drug target candidate. In a letter in *Nature Medicine*, Shen et al. argue that studying the downstream effects of ARID1A will produce insights that allow specific therapeutic intervention. They demonstrate that ARID1A helps to recruit MSH2 to chromatin during DNA replication and thus promotes DNA mismatch repair. Loss of ARID1A leads to a mismatch repair deficiency mutational signature dominated by C-to-T transitions, increased tumor mutational burden, and increased $CD8^+$ tumor-infiltrating lymphocytes with concomitant PD-L1 expression on tumor cells. In a mouse model of ovarian cancer, *ARID1A*-deficient tumors showed a superior response to anti-PD-L1 antibody treatment compared with control tumors. This finding suggests that ARID1A can contribute to the mutator phenotype in multiple cancer types and thus be relevant to immuno-oncology therapy.




*Nature Medicine* 2018;24:556–562; doi:10.1038/s41591-018-0012-z