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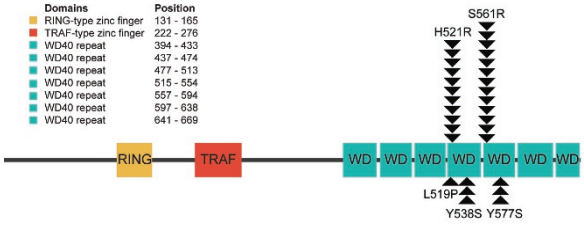
MODERN PATHOLOGY

TRAF7 mutations in adenomatoid tumors

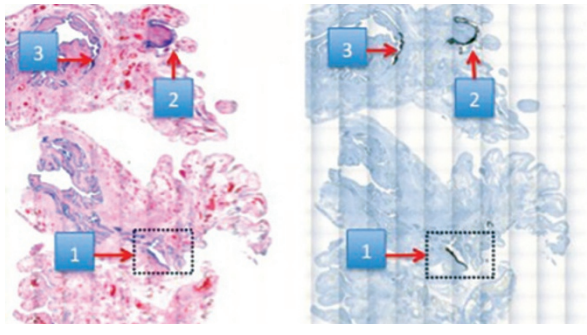
doi:10.1038/modpathol.2017.153



To investigate the molecular pathogenesis of adenomatoid tumors, Goode *et al* used genomic profiling on a cohort of 31 such tumors of the male and female genital tracts. All harbored somatic missense mutations in the five distinct hotspots in the C-terminally encoded WD40 repeats of *TRAF7*, an E3 ubiquitin ligase in the tumor necrosis factor receptor–associated factor (TRAF) family. *TRAF7* mutations were shown *in vitro* to drive aberrant NF-κB pathway activation. With documentation to support the fact that immune dysregulation may contribute to the development of these tumors, the group hypothesized that this could be due to selective pressure for the acquisition of activating *TRAF7* mutations or to potentiate the oncogenic effect of the mutations once acquired. The finding that all these tumors were defined by a set of mutations in the same gene, functionally driving the same pathway, provides a clear target for future study with regard to classification and therapeutic intervention.

Clonality in bilateral serous carcinomas

doi:10.1038/modpathol.2017.159



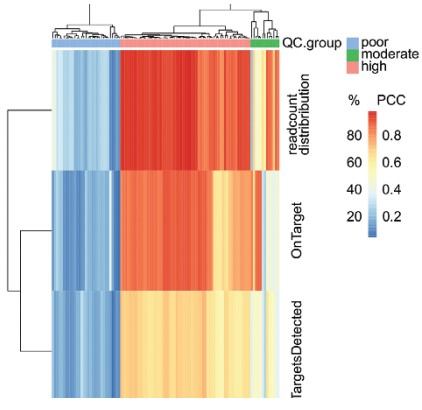
Singh *et al* assessed *TP53* mutations as a surrogate for the clonal nature of low-stage extrauterine high-grade serous carcinomas with multiple sites of involvement. *TP53* sequencing of tissue taken from each site in seven cases showed that the *TP53* mutations in the bilateral adnexal sites of involvement were identical. This clearly favors spread between adnexa rather than multifocal and independent tumor growth—even in the absence of clinically evident clonal peritoneal involvement. Thus, new considerations may be required to define these bilateral cases as stage II, reserving stage I for cases with unilateral and unifocal adnexal involvement. Stage assignment is controversial in these cases, and therapeutic options would not necessarily be affected by such an alteration in the stage. Nonetheless, these results could provide prognostic separation, especially key in the drive toward early detection.

LABORATORY INVESTIGATION

Transcriptome data from FFPE tissue

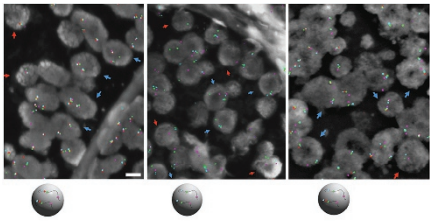
doi:10.1038/s41374-017-0001-8

Using formalin-fixed, paraffin-embedded (FFPE) prostate cancer samples, FitzGerald and colleagues sought to optimize transcriptome sequencing of RNA extracted from the fixed tissue. The optimization revealed the advantages of using fresh-cut 8-µm slides for microdissection and the use of a specific RNA isolation kit with 18 amplification cycles. The group adjusted variables in multiple pilot studies until they derived a protocol that enabled analysis of high-quality RNA from what would previously have been considered suboptimal FFPE tumor samples. The direction of change in gene expression of the top five genes identified was the same across 499 prostate adenocarcinomas in TCGA, with two of these genes previously described in prostate cancer biology. The method further enables use of FFPE-archived tissue banks in research on any cancer type for which fresh tissue acquisition for research is limited.



Deletion FISH analysis of tumor suppressor genes

doi:10.1038/s41374-017-0007-2



Fluorescence *in situ* hybridization (FISH) interpretation can be hindered by tissue sectioning and probe design that inhibits pattern recognition in formalin-fixed, paraffin-embedded (FFPE) samples. Yoshimoto and colleagues describe the use of common FISH methods in the detection of tumor suppressor gene deletions in human cancer and propose new probe designs that can recognize truncation artifacts with four-color *PTEN* FISH optimized for prostate cancer. Optimization techniques such as reduction in section thickness increase the frequency of signal truncation losses. One complicating factor of FISH and sequencing assays to assess gene deletions in cancer specimens is the infiltration of normal stroma and inflammatory cells, which reduces the sensitivity of DNA copy-number measurements. Based on their data, the group presents guiding principles for interpretation of FISH deletion assays in order to simplify interpretation and expand the use of this common clinical technique.

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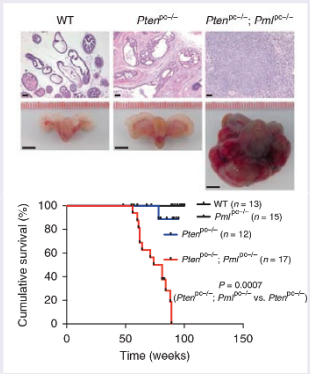
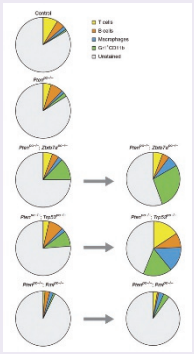
Lipogenesis in metastasis of prostate cancer



In investigating the role of lipids in metastatic human prostate cancer, Chen *et al* found that *PML* was frequently codeleted with *PTEN* and that conditional inactivation in mouse prostate altered the readout of indolent *Pten*-null tumors. ERK reactivation and subsequent hyperactivation of the SREBP prometastatic lipogenic pathway were features of *Pml* and *Pten* double-null prostate cancer. Blocking SREBP in vivo resulted in reduction of both tumor growth and metastasis. SREBP was shown to be downstream of *PML* loss–induced ERK activation, and fatostatin's inhibition of lipogenesis resulted in reduced growth and metastasis *in vivo* despite *PML* loss. A high-fat diet increased lipid accumulation in prostate tumors that was sufficient to drive metastasis in a previously nonmetastatic *Pten*-null mouse model.

Nature Genetics 2018;50:206–218; doi:10.1038/s41588-017-0027-2

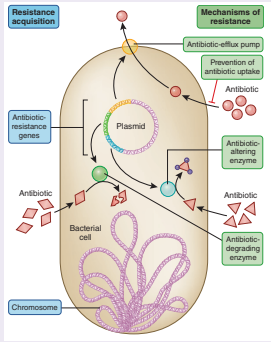
Immune landscapes influence tumor progression



Bezzi *et al* investigated how immune states of the tumor microenvironment influence progression and metastasis through immunosuppression. Using *Pten*-loss prostate cancer as a model, either alone or in combination with loss of *Trp53*, *Zbtb7a*, or *Pml*, they identified distinct heterogeneity in these infiltrated landscapes. *Zbtb7a* transcriptionally represses granulocyte attractant CXCL5, which is upregulated in $Pten^{pc-/-}$; $Zbtb7a^{p-/-}$ tumors, whereas loss of p53 leads to upregulated expression of Gr-1^{+}CD11b cell attractant CXCL17. Assessing these different genetic backgrounds revealed distinct patterns of immune cell distribution, ranging from barren to heavy infiltration. These observations were supported by analysis of human prostate cancer specimens. The group proposes that successful clinical trials and precision therapeutics for these cancers will be designed only by taking genotypic–immunophenotypic analyses into account.

Nature Medicine 2018; 24:165–175; doi:10.1038/nm.4463

Vaccines to prevent antimicrobial resistance



The morbidity and mortality associated with the rise in antimicrobial resistance due to bacterial pathogens have reached alarming levels. Effective immunization can reduce the use of antibiotics and, even with such use, can slow the associated rise in antimicrobial resistance. Strategies currently under development by the World Health Organization to combat antimicrobial resistance encompass a range of modalities. In the assessment of Jansen *et al*, vaccines are an underrecognized resource despite documented successes. The influenza vaccine, for example, is known to combat not only influenza but other secondary bacterial infections, such as pneumonia and otitis media, indicating that the expensive and long-term work that goes into establishing new vaccines, in addition to being necessary in its own right, can lead to protection against antimicrobial resistance. Vaccine development is one side of the global issue; the other side is maintaining and creating new markets to ensure commercial viability.

Nature Medicine 2018;24:10–19; doi:10.1038/nm.4465

Emma Judson contributed to these reviews.