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MODERN PATHOLOGY

Inferior survival related to *TP53* aberration

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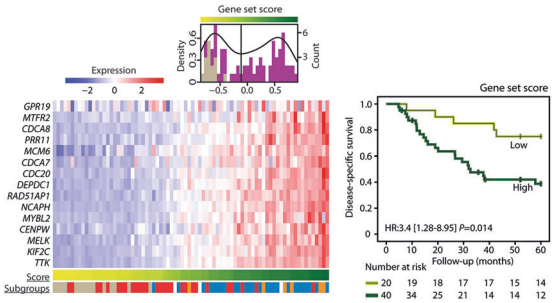
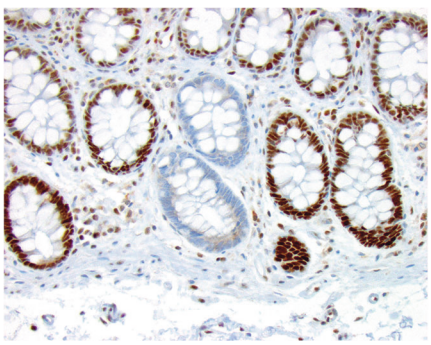


To assess the role of *TP53* in the development of malignant peripheral nerve sheath tumors, Høland et al. took on a multilevel molecular study of aberrations in the TP53 network in relation to patient outcomes. Of 98 malignant peripheral nerve sheath tumors, 8.2% showed point mutations in *TP53* with loss of heterozygosity and loss of protein function, with *MDM2* amplification in an additional 5.5%. A third of the tumors in the cohort had loss of a chromosomal region containing *TP53*; none had complete loss of the locus. The two mutational patterns were mutually exclusive and correlated with prognosis. Using a *TP53*-associated gene signature, the group identified an expression profile that was indicative of poor prognosis for these tumors and was present in 60% of those in the study. The investigators propose that new treatment opportunities could be identified by targeting the pathways represented in the profile.

Novel diagnostic tool for Lynch syndrome

doi:10.1038/s41379-018-0079-6

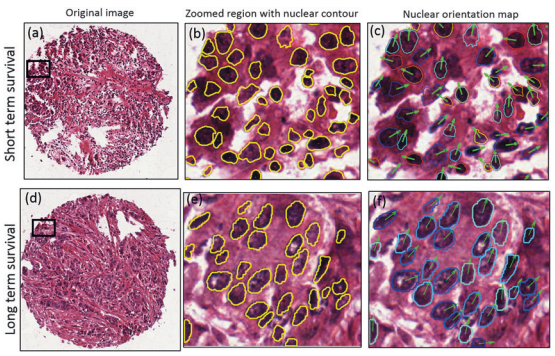


Pai et al. sought to determine whether DNA mismatch repair (MMR) protein-deficient non-neoplastic intestinal crypts could be used to identify patients with Lynch syndrome, given the challenge of distinguishing between sporadic MMR protein deficiency and true Lynch syndrome in the absence of germline molecular assessment. While there was no significant difference in the number of non-neoplastic intestinal crypts between patients with and without Lynch syndrome, MMR protein–deficient colonic crypts were observed in 35% patients with Lynch syndrome compared with 1% of patients in the control group. The authors propose that abnormal MMR protein expression should no longer be considered sufficient for a diagnosis of Lynch syndrome because a subset will exhibit no evidence of germline alterations in DNA MMR genes; these patients should be considered to have Lynch-like syndrome. The challenge noted is that additional sampling of non-neoplastic colorectal mucosa may be required in order to detect the MMR protein–deficient colonic crypts.

LABORATORY INVESTIGATION

Nuclear orientation analysis predicts survival of ER+ breast cancers

doi:10.1038/s41374-018-0095-7

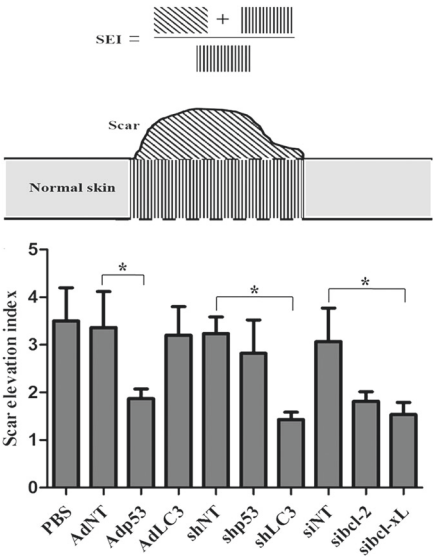


The ability to identify which early-stage estrogen-positive (ER+) breast cancer patients will benefit from adjuvant chemotherapy would have extensive implications given the prevalence of the diagnosis in the United States. Lu et al. used a tissue microarray and quantitative computer-extracted image features to identify nuclear pleomorphism on the basis of 615 features and correlated them with disease outcome. Among short-term-survival patients there was greater variation in nuclear orientation, whereas the long-term-survival population exhibited uniform orientation. When the researchers used their image classifier alone to identify high-risk patients, they found correlation with significantly

poorer survival. Using a combination of T-stage, histology grade, and nuclear grade, they showed that their image classifier was independently predictive of poorer survival, a crucial step in influencing treatment decisions for these patients.

New molecular targets in therapeutics for hypertrophic scarring

doi:10.1038/s41374-018-0099-3

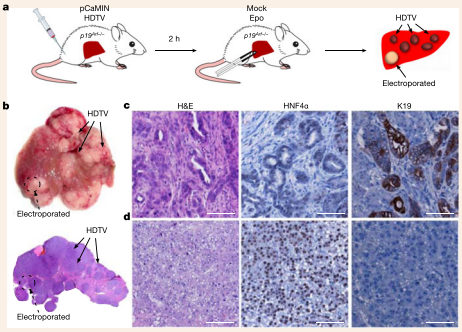


Shi et al. have previously investigated the dysregulation of autophagy in hypertrophic scar formation and its role in fibrosis during this process. As their next step, they sought to further investigate the role of p53-modulated autophagy in the process. Overexpression of wild-type p53 (Adp53) limited collagen and α-SMA expression in hypertrophic scars, promoting autophagic capacity through altered Bcl-2 and Bcl-xL expression. Silencing Bcl-xL, Bcl-2, and Adp53 resulted in increased apoptosis of the hypertrophic scar fibroblasts (HSFs), indicating that wild-type p53 inhibited fibrosis by regulating autophagy-driven apoptosis in the scars. Potentially more significant was the observation that silencing Bcl-xL had antifibrotic effects in a rabbit ear scar model; however, inhibition of autophagy was also seen. Inhibition of these pathways suggests a variety of new potential molecular targets for the treatment of hypertrophic scarring.

nature.com/pathology

Cell-death microenvironment directs lineage commitment

Liver carcinomas often develop in chronically damaged livers where some form of cell death has occurred. To elucidate these different forms of cell death and their role, Seehawer et al. developed in vivo models of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) using transposon mouse models and then performed in vivo lineage tracing to reveal the hepatic origins of ICC. Using western blot analyses for cleaved caspase-3, hydrodynamic tail vein infection to force expression of oncogenes such as *Myc* was shown to predominantly induce apoptosis rather than necroptosis, which has been described in other liver diseases.

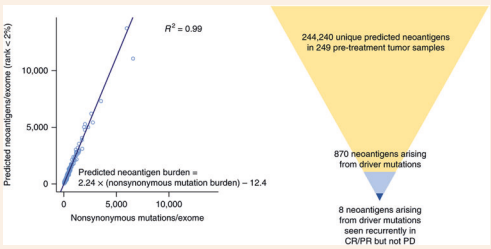


The group also found that HCC and ICC were defined by unique epigenetic signatures when they were unable to identify spontaneously acquired mutations that would account for the difference in growth between the two models. Chromatin accessibility was significantly different between HCC and ICC cell lines, and further work is needed to model the intracellular signaling cascades in hepatocytes that mediate epigenetic regulation of the lineage commitment factors *Tbx3* and *Prdm5* expression in ICC and HCC.

Nature, published online 12 September 2018; doi:10.1038/s41586-018-0519-y

Population studies to assess response to immune checkpoint blockade

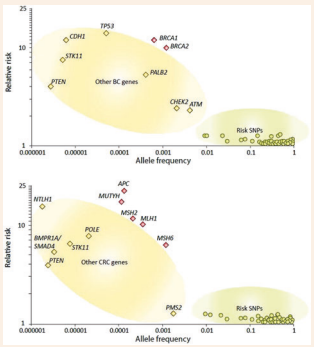
Response to immune checkpoint blockade correlates with tumor mutational burden. Miao et al. sought to lay out methods for analyzing large clinical cohorts to generate clinically predictive features of response to immune checkpoint blockade. Patients with complete or partial response to inhibition of programmed cell death protein 1 (PD-1) had significantly higher tumor mutational burdens than patients with progressive disease, both within cancer types and when broken down by treatment with PD-1 or PD-L1 inhibitors. Patients with stable disease fell between the two ranges. The study also identified mutations in specific genes, along with copy-number alterations, that were associated with response or resistance to these therapeutics. *KRAS* and *EGFR* mutations in lung cancer, in conjunction with carcinogenic exposure, intratumoral heterogeneity, and mutational burden, could be used to demonstrate response or resistance. Ultimately, neoantigens were predicted from the mutations, and a few of the recurrent neoantigens correlated with outcome.



Nature Genetics 2018;50:1271–1281; doi:10.1038/s41588-018-0200-2

Population testing: new wave in cancer genetics

Turnbull et al. propose the initiation of national population-testing programs to identify carriers of first-wave gene mutation carriers such as *BRCA1*, *BRCA2*, *MLH1*, and *MSH2* in order to optimize screening, prevention, and early detection of cancers. With the genomic architecture much more highly complex than previously thought, a second wave of such susceptibility genes does not appear to be forthcoming without much larger experiments. These might, due to increasing affordability of high-throughput sequencing, lead to clear associations of a gene with a specific cancer, as well as the penetrance of the mutation, and therefore inferences about risk and the implied pathogenicity. Thus, with large-scale population-level genetic testing, the group suggests that there is value in deeply assessing known cancer genes rather than focusing on identifying new genes for which poorly characterized risk and questionable disease association limit the gains.



Nature Genetics 2018;50:1212–1218; doi:10.1038/s41588-018-0202-0