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MODERN PATHOLOGY

Two-stain screening may miss Lynch syndrome

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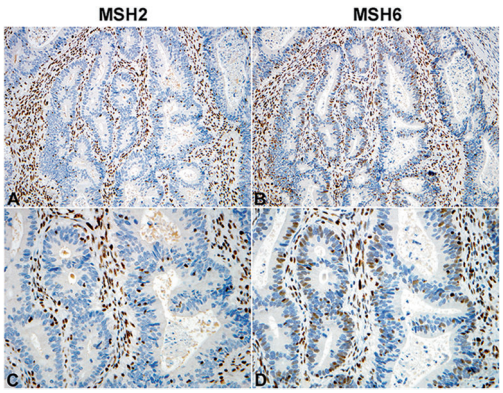

The two-stain method for Lynch syndrome screening relies on immunohistochemistry for just two mismatch repair proteins (MSH6 and PMS2), with reflex testing of the partner stain (MSH2 and MLH1, respectively) if either is absent. Pearlman et al. found that this method misses cases of Lynch syndrome. They performed next-generation sequencing (NGS) of germline DNA for mismatch repair genes, followed by tumor next-generation sequencing for somatic mutations in 495 cases. Thirty-three MSH2-absent cases were identified using immunohistochemistry, 14 of which had no MSH6 expression, 8 had ambiguous staining, and 11 had convincing MSH6 expression. The great majority of these cases (27 of 33) had mutated *MSH2* on NGS analysis. Thus, the two-stain method fails to identify every patient with Lynch syndrome; the subjective nature of interpreting the staining is combined with the inability of the MSH6 (with PMS2) to detect all cases in which MSH2 is absent or *MSH2* is mutated. The authors recommend a four-stain method for optimal screening for Lynch syndrome.

Novel metrics for MSI in colorectal adenocarcinoma

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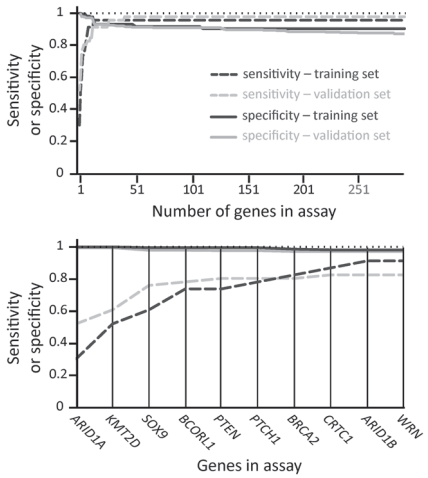
Papke et al. developed a sequencing-based metric aimed at distinguishing mismatch repair (MMR)-deficient from MMR-proficient colorectal adenocarcinomas and compared it directly with immunohistochemical staining. Only a single criterion—three or more single base pair insertion/deletion mutations per megabase, potentially on panels as small as approximately 50 genes—was sufficient to detect MMR-deficient colorectal adenocarcinomas with sensitivity and specificity of 96 and 99%, respectively. Information from only the genes *ARIDIA*, *KMT2D*, and *SOX9* was equally specific, but specificity dropped to 76%. As



compared with traditional PCR, next-generation sequencing allows shorter DNA repeats to be analyzed at high throughput with a high degree of discrimination to distinguish MMR-deficient and -proficient tumors, with implications for diagnosis and treatment decisions. Additional study is needed to confirm these findings and determine whether similar approaches are applicable to other tumor types in which DNA mismatch deficiency is encountered.

LABORATORY INVESTIGATION

APOE affects bone mass

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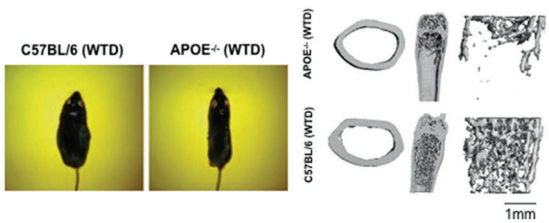

Apolipoprotein A-1 (APOA1) and APOE have been studied in the context of fat and bone metabolism. Papachristou et al. investigated the mechanism of APOE in bone metabolism. In APOE knockout mice fed a Western-type diet, bone mass was reduced compared with their wild-type counterparts, and body weight was significantly reduced. Static and dynamic histomorphometry revealed a decrease in osteoblastic bone synthesis in the $APOE^{-/-}$ mice, with RUNX2 levels significantly reduced while RANKL and its ligand were significantly increased. The finding of increased collagen 1a in the $APOE^{-/-}$ mice, along with the other data, indicated that these alterations in the cross-linking of collagens could cause the subsequent lack of elasticity.

The data also suggested that further in vitro studies might confirm APOE as a target for the treatment of osteoporosis as well as obesity.

Secretome control of metastatic progression of NSCLC

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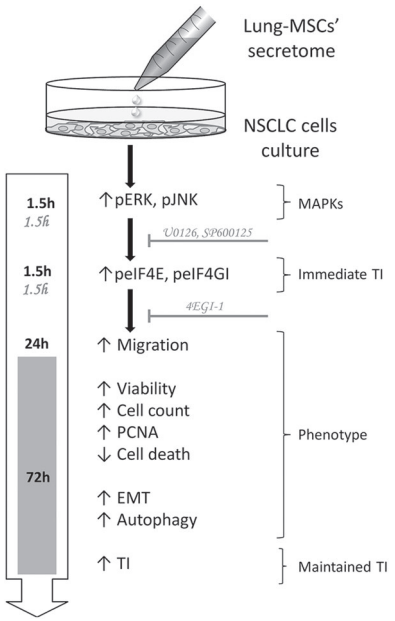

Attar-Schneider et al. expand on data that they had previously published on mesenchymal stem cells (MSCs) and their deleterious effect on non-small-cell lung cancer (NSCLC) cells. NSCLC cell lines cultured with healthy/NSCLC MSC–conditioned media (secretome) were shown to induce NSCLC cell viability and proliferation while inhibiting cell death. Matrix metalloproteinases, promoting an aggressive course of NSCLC with a role in extracellular matrix degradation that allows migration, were found in significantly higher levels compared with cell-free medium. Increased translational activity, proliferation, migration, and autophagy were all more prominent in NSCLC cells treated with the secretome of NSCLC-derived MSCs. While additional studies are needed to establish the role of autophagy, the compiled data indicate that lung MSCs differ from metastatic bone MSCs, a finding that might lead to identification of targetable signals to control metastatic progression in NSCLC.

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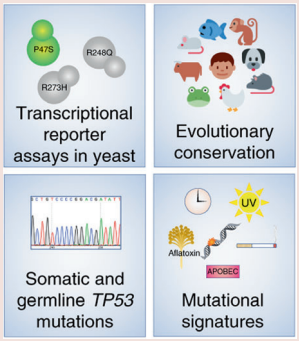
TP53 and cancer mutational processes

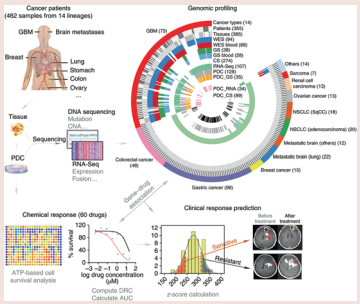
Giacomelli et al. report that deletion of endogenous wild-type, but not mutant, *TP53*, enhanced the fitness of human cancer cells, preventing cell death induced by etoposide. Enrichment screens and massively parallel sequencing showed that alleles with silent mutations were significantly depleted in $p53^{NULL}$ cells treated with nutlin-3 and enriched when treated with etoposide, relative to alleles with premature stop codons. Tissue of origin had signature *TP53* mutations that correlated with specific mutational processes. Five residues (Arg273, Arg248, Arg175, Arg282, and Gly245) had missense mutations in 30% of all assays, indicating a key role, although no *TP53* dependency was shown in cancer cell lines harboring these hotspot mutations, indicating these sites might simply be inherently mutable. More than 80% of full-length p53 missense mutants with loss of function also displayed dominant negative activity; this suggests that the ability of mutant p53 to interfere with wild-type p53 is a crucial factor in tumorigenesis.



Nature Genetics 2018;50:1381–1387; doi:10.1038/s41588-018-0204-y

Targeted therapeutics model

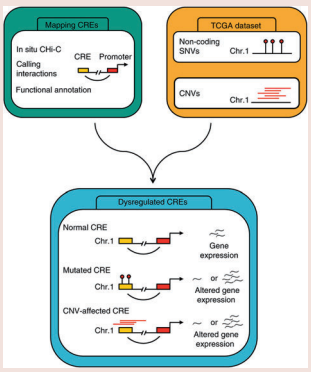
Finding the key to patient-tailored therapy is a goal of cancer therapeutic development. Lee et al. compiled the pharmacological landscapes of 462 patient-derived tumor cells (PDCs) across 27,720 drug-PDC combinations. They identified distinct groups of compounds with high and low half-maximal inhibitory concentrations, suggesting a strong association between pharmacological drug response and genomic aberration. This enabled the group to identify cell types most likely to respond to compounds. Ibrutinib, previously shown to have an antitumor effect in non-small-cell lung cancer cells, was exclusively beneficial to those with the *EGFR* T790M mutation, which is associated with erlotinib resistance. Other *EGFR* mutations were significantly linked to increased efficacy of ibrutinib. A role for ibrutinib in EGFR-driven gliomas was also suggested. Targeted therapeutics is often hampered by feasibility, and the PDC models described here facilitate screening for drug sensitivity in order to optimize clinical trial design.



Nature Genetics 2018;50:1399–1411; doi:10.1038/s41588-018-0209-6

Identification of noncoding drivers of CRC

Orlando et al. used high-throughput chromosome conformation capture (Hi-C) techniques for 19,023 promoter fragments to search the genome for cis-regulatory elements (CREs) that might harbor cancer-driving mutations. They identified a recurrently mutated CRE that interacted with the *ETV1* promoter and affected gene expression where amplification of another CRE upregulated *RASL11A* expression. Levels of *ETV1* and *RASL11A* were shown to be associated with differential cell growth, and, while the role of *RASL11A* in tumorigenesis has not been established, the group confirmed its interaction in a panel of colorectal carcinoma cell lines. Patient survival data confirmed that high levels of *ETV1* expression were associated with poorer relapse-free and overall survival, but no effect on patient outcome was noted for *RASL11A*. The effects of gene promoters on cancer development and progression are understudied, and approaches such as this will provide vital knowledge.



Nature Genetics 2018;50:1375–1380; doi:10.1038/s41588-018-0211-z