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MODERN PATHOLOGY

Therapeutic resistance in intraductal pancreatic cancer

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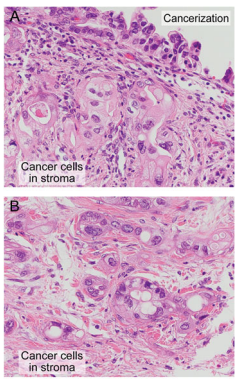

To explore the mechanisms of resistance to neoadjuvant chemotherapy (NAC) in borderline resectable and locally advanced pancreatic ductal adenocarcinoma (PDAC), Fujikara et al. hypothesized that the location of residual neoplastic cells plays a role. PDAC cells are known to invade the stroma but also to invade back into and spread via the pancreatic ducts in a process called cancerization of ducts (COD). The team compared responsiveness to chemotherapy of cells in the two locations using tissue from pancreatic resections of 174 PDAC patients (97 NAC and 77 who had had immediate surgery). COD was identified at the same prevalence in both groups; however, the proportions of cancer cells that were intraductal were significantly different and highest in patients with a marked response to therapy. These data indicate that intraductal components of PDAC are significantly less responsive to chemotherapy and could have a role in therapeutic resistance, even following successful significant debulking surgery.

Interdisciplinary care of patients with DCS

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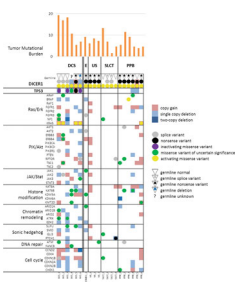

Kamihara et al. analyzed six *DICER1*-associated central nervous system sarcoma (DCS) tumors and 14 other *DICER1*-associated tumors. Histologic, immunohistologic, and molecular features were all assessed with the aim of better understanding this newly identified rare childhood sarcoma. Tumor mutational burden was significantly higher in the six DCS tumors than in the other 14 tumors examined, with biallelic *DICER1* variants identified in all cases and germline variants in two of the five that were tested; these two patients and one other had all had previous neoplasms. The DCS tumors also exhibited genomic alterations enriched for potentially targetable pathways such as Ras activation and *TP53* inactivation. Two of the six patients with DCS developed lung tumors, and sequencing confirmed clonal similarity to the DCS, indicating metastasis rather than a second primary tumor. The incidence of this metastatic location suggests a role for chest imaging in follow-up surveillance in primary DCS. The study findings indicate that interdisciplinary care is crucial in the management of patients with DCS.

LABORATORY INVESTIGATION

Predicting GBM subgroups and association with clinical outcomes

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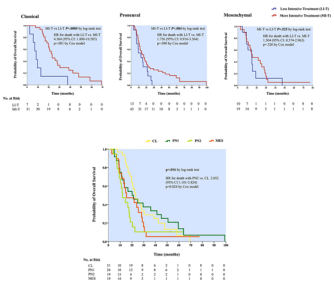

Glioblastomas (GBMs) can be classified into three transcriptional subgroups—proneural, mesenchymal, and classical—with different molecular alterations, prognosis, and response to therapy. Because stratifying GBMs into these subgroups is not always straightforward, Orzan and colleagues propose a machine-learning algorithm and integrated molecular and immunohistochemical approach. The intriguing feature of the new model is that when it was compared with standard methods of stratifying patients, the mesenchymal and classical subgroups were well classified but the proneural group showed mixed proneural/classical phenotypes. Even where the algorithm classified tumors as

proneural, the samples showed equal probability of being classical. In deeper analysis these ambiguous samples showed high expression of epidermal growth factor receptor and patients had lower survival. The group proposes that with further validation they will be able to develop a more efficient method for predicting subgroups with high accuracy and with significant association with clinical outcomes.

A whole transcriptome signature for prognostic prediction

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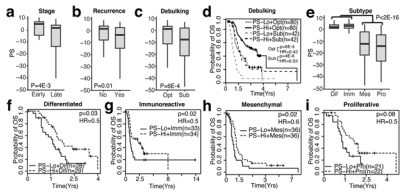

The ability to accurately predict survival of cancer patients with noninvasive techniques is increasingly crucial in clinical research and practice. Despite large numbers of potential transcript signatures, such models have not made their way into routine clinical practice. Schaafsma et al. describe a generic RNA sequencing platform for prognostic prediction using ovarian and lung adenocarcinoma that may be applicable across disease types, and its utility might extend outside of oncology. Their ovarian cancer signature was predictive of patient survival and added additional prognostic value in six independent datasets; they also found that it could stratify individual clinical variables such as level of differentiation or proliferation, subtype, and the presence of immunoreactive or mesenchymal phenotypes. While they acknowledge limitations of their system, they propose further evaluation and additional wide-ranging implications for predicting a patient's likely prognosis on multiple parameters in one assay.

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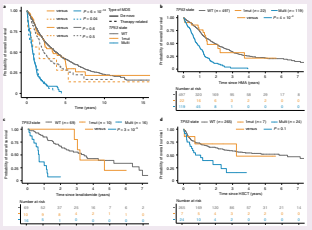
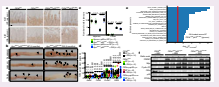
Implications of *TP53* allelic state in MDS



Establishing the allelic state of tumor protein 53 (*TP53*) mutation and investigating it in relation to disease development, treatment responses, and outcomes have not previously been undertaken. In this study, 3324 patients with myelodysplastic syndromes (MDS) were analyzed for *TP53* mutations and allelic imbalances. One-third of the patients had monoallelic mutations; these patients did not differ from *TP53* wild-type patients in outcomes or response to therapy. The two-thirds of patients who exhibited biallelic targeting (multi-hit) had high-risk presentations, poor outcomes, and increased predictive risk of death and leukemic transformation. The *TP53* allelic state also correlated with contrasting levels of genome stability and patterns of co-mutation, with their own implications. These findings led the group to propose that allelic state is a crucial prognostic and diagnostic marker in MDS decision-making. Future correlative studies of treatment response to further validate these results across cancer indications are required.

Nature Medicine, published 3 August 2020; https://doi.org/10.1038/s41591-020-1008-z

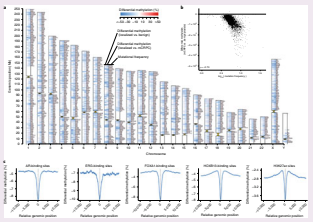
Plasticity of p53 is influenced by gut microbiome



Kadosh et al. explored the role of p53 in gastric cancer in mice and found that the location within the gut influenced the oncogenic effect of p53. In the distal gut, mutant p53 had its established oncogenic effect, but in the proximal gut and in tumor organoids, it had a pronounced tumor-suppressive effect. Mutant p53 in these locations eliminated dysplasia and tumorigenesis and promoted normal growth and differentiation. A single metabolite from the gut microbiota—gallic acid—was shown to be responsible for maintaining these effects. The finding was reversed in gut-sterilized mice and was rescued by the return of the microbiome. This study highlights the plasticity of even a seemingly well-known cancer mutation and illustrates a crucial role of the microenvironment in its functional outcome.

Nature, published 29 July 2020; https://doi.org/10.1038/s41586-020-2541-0

DNA methylation in advanced prostate cancer



DNA methylation is a known regulator of gene expression, but its role in metastatic cancer is unknown. Zhao and colleagues conducted a large integrated study of whole-genome, whole-methylome, and whole-transcriptome sequencing in metastatic cancer using 100 castration-resistant prostate metastases. The results revealed alterations that were only detectable at this overarching level. Twenty-two percent of tumors exhibited a novel epigenomic subtype of hypermethylation and somatic mutations in *TET2*, *DNMT3B*, *IDH1*, and *BRAF*. The group also identified intergenic regions where methylation is associated with RNA expression of the oncogenic driver genes *AR*, *MYC*, and *ERG* by illustrating the interplay between methylation and DNA structure to bring regions into proximity. Differential methylation during progression also preferentially occurred at somatic mutational hotspots and putative regulatory regions. Widespread investigations using multidisciplinary tools such as this are critical for investigating the role of methylation in other tumors and determining their impact on gene expression.

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Emma Judson contributed to these reviews.