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MODERN PATHOLOGY

Pathologist–AI synergy in Gleason grading

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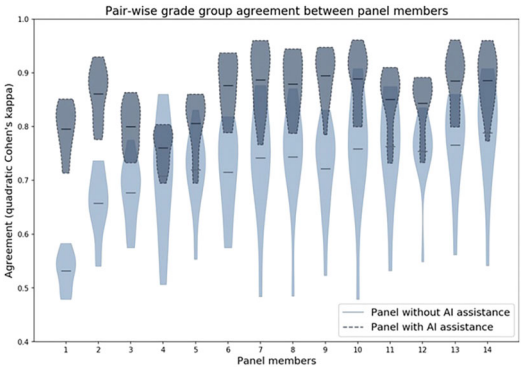

Bulten et al. developed an artificial intelligence (AI) system that would use deep learning to remove pathologist-level observer variability from calculation of Gleason scores in prostate cancer patient prognosis. Acknowledging that artifacts, foreign tissue, and other anomalies can reduce the efficacy of systems such as these, they proposed the synergistic integration of AI systems with pathologists' experience. Using AI across 14 observers and 160 biopsies, they demonstrated that agreement of the panel with an expert reference standard increased significantly. Even in an external validation panel, the group demonstrated that AI-assisted pathologists outperformed unassisted pathologists as well as stand-alone AI systems. While acknowledging the limitations of their data sets, they indicate that no other studies have been performed to investigate this potentially important tool in prostate cancer prognosis.

MHC class I loss is a resistance mechanism for immunotherapy

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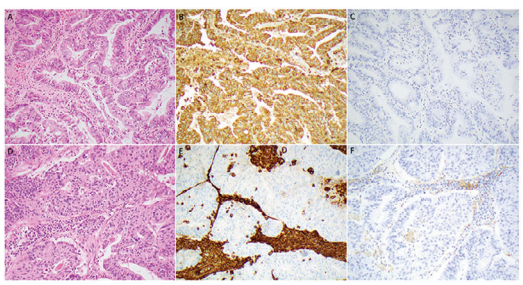

Friedman et al. investigated major histocompatibility complex (MHC) class I loss as a mechanism of immunotherapeutic resistance, even among cancers that appear to be good candidates for checkpoint inhibition. MHC class I is a membrane-bound protein complex, the loss of which has been shown to decrease tumor neoantigen presentation to the immune system. The authors examined MHC class I expression in a range of endometrial carcinomas, including MMR-deficient and PD-L1-positive tumors (the obvious candidates for immunotherapy). Forty-two percent of the tumors (including 46% MMR-deficient and 25% PD-L1-positive) showed loss of MHC class I expression in either a subclonal (26%) or diffuse (16%) pattern. The group concluded that tumoral MHC class I status, irrespective of mismatch repair status, may be an important factor in selecting patients most likely to respond favorably to checkpoint inhibition.

LABORATORY INVESTIGATION

NO depletion and antitumoral therapeutics in ER$^+$ breast cancer patients

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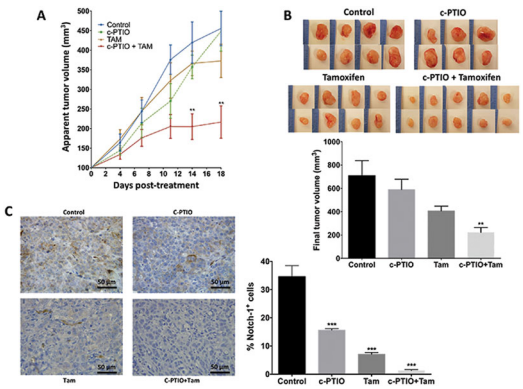

Cancer stem cells (CSCs) are involved in resistance of estrogen (ER)-positive breast tumors against endocrine therapies such as tamoxifen. López-Sánchez et al. investigated the potential role of nitric oxide (NO) in CSC biology and its contribution to resistance to antihormonal therapy in ER$^+$ breast cancer. Analyzing mammosphere-formation capacity and using an orthotopic breast tumor model in mice, the group investigated NO depletion and NOS2 silencing in order to assess efficacy of the NO-targeted therapy in combination with tamoxifen. They found that NO depletion inhibited mammosphere

formation and increased antitumoral efficacy of tamoxifen in ER$^+$ breast cancer cells and that low NOS2 expression was significantly associated with a higher metastasis-free survival in ER$^+$ breast cancer patients treated with tamoxifen. The group proposes the addition of NO-targeted therapy to antihormonal therapeutics in patients with ER$^+$ breast cancer, not only to improve efficacy but also to avoid the development of resistance to either therapeutic strategy.

Patient-derived explants in drug discovery

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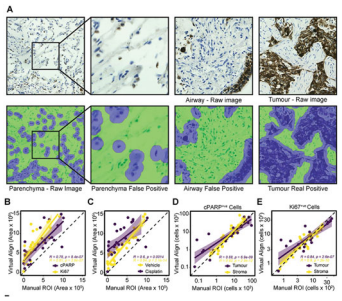

Cancers are known to be heterogeneous in nature, yet many in vitro models rely on single cell lines in spheroid or xenograft models. Miles et al. investigated the use of patient-derived explants (PDEs) to directly culture fragments of freshly resected tumor tissue, maintaining the original architecture of the tumor. This model allows the tumor microenvironment and tumor heterogeneity to be considered in investigations of drug responses. Immunostaining of validated biomarkers was quantitatively and qualitatively evaluated, and the process was automated to enhance assessment of multiple markers across the explant by virtual double-staining. Taken together, these results may provide new tools and automation for increasing throughput of the PDE–drug discovery pipeline.

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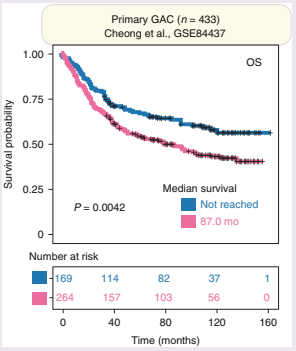
12-Gene prognostic signature of ITH in gastric adenocarcinoma

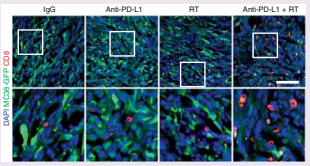
Although intratumoral heterogeneity (ITH) is a recognized feature of cancer, its origins are not well understood. Wang et al. performed single-cell transcriptome profiling of peritoneal carcinomatosis (PC) in 15 patients with gastric adenocarcinoma (GAC). The group was able to distinguish cell types at the transcriptomic, genotypic, molecular, and phenotypic levels. Using single-cell analysis of ITH, they classified PC specimens into two subtypes that were prognostically independent of clinical variables. A 12-gene prognostic signature was derived and validated across multiple large-scale GAC cohorts, and the authors propose that it can be used in prognostic stratification of patients given that it correlated with tumor-cell lineage (GI-mixed vs gastric-dominant) as well as patient survival.



Nature Medicine 2021;27:141–151; https://doi.org/10.1038/s41591-020-1125-8

Radiotherapy restores efficacy of immunotherapy for liver metastases

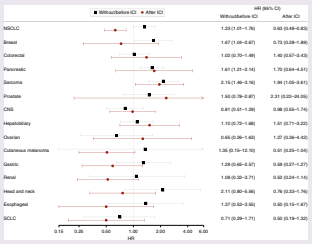
Yu et al. investigated the mechanism for the decrease in efficacy of immunotherapy observed in patients with liver metastases, and their findings implicated macrophage-mediated T-cell elimination. Within the liver metastases in mouse models, activated CD8$^+$ T cells are siphoned from the circulatory system and undergo apoptosis following interaction with FasL$^+$CD11b$^+$F4/80$^+$ monocyte-derived macrophages. This trend was mirrored in patients in whom reduced peripheral T-cell numbers and diminished tumoral T-cell diversity were observed. The authors demonstrated that liver-directed radiotherapy eliminates these immunosuppressive hepatic macrophages by increasing hepatic T-cell infiltration, reducing liver myeloid cell numbers, and lowering the ratio of CD11b$^+$F4/80$^+$ myeloid cells to CD8$^+$ T cells. They suggest that the presence of liver metastases is a factor in predicting which patients will benefit from immunotherapy. They also propose that combining liver-directed radiotherapy with immunotherapy could enhance the efficacy of both treatments in patients with liver metastases.



Nature Medicine 2021;27:152–164; https://doi.org/10.1038/s41591-020-1131-x

Treatment context impacts association of tumor mutational burden with prognosis

In the context of treatment with immune checkpoint inhibitors (ICIs), longer survival is associated with a high tumor mutational burden (TMB) in multiple cancer types. Valero et al. sought to determine whether this is true outside of immunotherapy. They analyzed 10,233 patients (80% non-ICI-treated, 20% ICI-treated) across 17 cancer types. The authors were careful with their patient selection, considering that for some tumor types immunotherapy is first-line therapy and that survival expectations differ for different cancer types. As they had suspected, in ICI-treated patients higher TMB was associated with longer survival, although not in every cancer type. Intriguingly, in many cancer types the opposite was found to be true, and in non-ICI-treated patients higher TMB was not associated with better prognosis.



Nature Genetics 2021;53:11–15; https://doi.org/10.1038/s41588-020-00752-4

Emma Judson contributed to these reviews.