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MODERN PATHOLOGY

Call to standardize diagnosis of invasive lobular breast cancer

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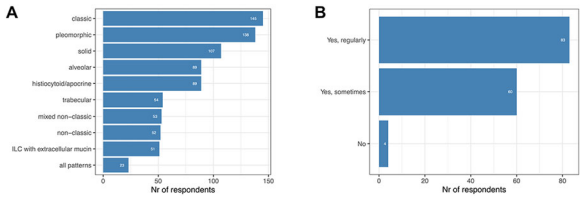

De Schepper et al. explored current practices surrounding the diagnosis of breast cancer as invasive lobular carcinoma (ILC), which accounts for 15% of breast cancer cases. Although loss of cell adhesion due to functional inactivation of E-cadherin is a hallmark of ILC, current World Health Organization guidelines do not require that E-cadherin loss be demonstrated by immunohistochemistry (IHC). Two large, randomized trials have demonstrated overdiagnosis of ILC, with only ~60% of cases confirmed by central pathology. The group sent a questionnaire to pathologists worldwide over 6 months to assess various pathological determinants of ILC diagnosis. The results showed that roughly half of the institutions used loss of E-cadherin expression as determined by IHC in their diagnostic protocols, although the wide variability in IHC protocols caused variations in both results and interpretation. With clinical trials evaluating diagnosis-specific therapeutic options, diagnostic standardization for ILC is crucial for optimal patient care.

PD-L1, TIM-3, and B7-H3 as potential therapeutic targets in ESC

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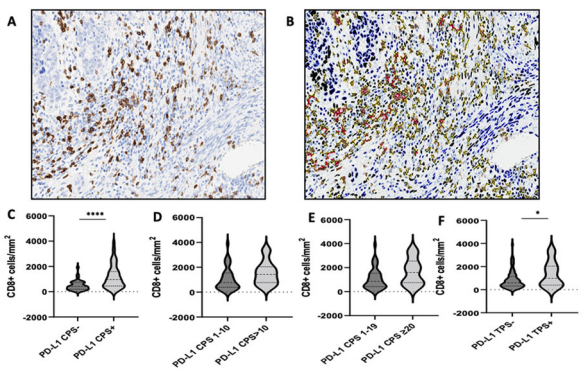

Despite the use of immune checkpoint blockade as a therapeutic option for endometrial cancers, data on the expression of immune checkpoints in endometrial serous carcinoma (ESC) are limited. Chen et al. determined the prevalence and prognostic significance of PD-L1, TIM-3, and B7-H3 in 99 ESCs as well as correlation with $CD8^+$ tumor-infiltrating lymphocytes. The three were expressed at 17%, 10%, and 93% of cases, respectively, using a tumor proportion score (TPS) with a cutoff of 1%. No association between PD-L1 or TIM-3 expression and survival was found using TPS, although both correlated with higher $CD8^+$ T-cell density. Combined positive score, but not TPS, correlated with overall survival. The data suggest support for immune checkpoint blockade in ESC and may inform design of future clinical trials along with the selection and development of individualized therapeutics for these patients.

LABORATORY INVESTIGATION

c-Jun induction predicts delayed DNA repair in cisplatin-treated cells

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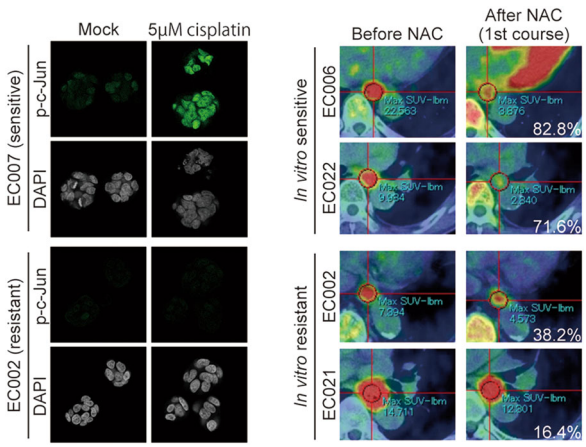

The search for functional, predictive biomarkers for cancer therapy is challenging despite advances in sequencing technology and large-scale drug screenings across hundreds of cell lines. Tsukamoto et al. studied sensitivity-specific change in the phosphorylation state of signaling molecules and developed a method for predicting responses to cisplatin in patient-derived tumor organoids (PDOs). Across a panel of biomarkers, they observed that cisplatin-sensitive cell lines or PDOs showed enhanced phosphorylation of c-Jun (p-c-Jun) within 24 hours after cisplatin exposure. In comparisons of responses to cisplatin in a neoadjuvant setting (docetaxel/cisplatin/5-fluorouracil) in six matched patients, c-Jun induction was shown to be downstream of tumor necrosis factor

signaling induced by the cisplatin and predictive of delayed DNA repair in cisplatin-treated cells. Following confirmation in a larger cohort, enhanced c-Jun phosphorylation in response to cisplatin might be a predictive biomarker of cisplatin efficacy.

Coupling of MALDI-MSI, WES, and RNA-seq from FFPE sections

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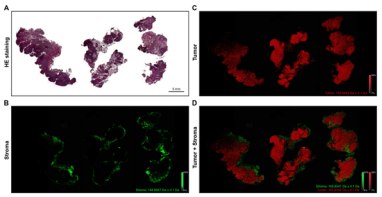
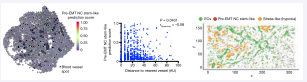


Kreutzer et al. performed simultaneous matrix-assisted laser desorption ionization mass spectrometry imaging (MALDI-MSI), whole-exome sequencing (WES), and RNA sequencing from the same formalin-fixed paraffin-embedded (FFPE) tissue sections. Genomic DNA and total RNA were extracted from untreated, hematoxylin-eosin-stained and MALDI-MSI-analyzed FFPE tissue sections from three head and neck squamous carcinomas. Across the platforms the data met the accepted quality criteria. The team validated their data sets and demonstrated that tumor mutational burden was in the same range for tissues from the same patient with overlapping mutational signatures. The group propose that their data show that simultaneous molecular profiling of MALDI-MSI-processed FFPE tissue samples, even at transcriptome and exome levels, is feasible and reliable. This supports the search for novel biomarkers and other targets for diagnostics and therapeutics.

nature.com/pathology

Distinction of cells providing growth from metastasis in melanoma

Melanoma is a notoriously heterogeneous and plastic disease with high cell-state diversity. Karras et al. used a series of assays including lineage tracing and single-cell and spatial transcriptomics to produce a hierarchical model of tumor growth. It revealed that only a fraction of cells are fated to become involved in primary tumor growth, while others are able to remain plastic enough to switch identities while disseminating to secondary organs and therefore play a role in metastasis. The group produced a spatially and temporally resolved map of the diversity and trajectories of melanoma cell states with phenotypic competencies acquired after exposure to specific niche signals. They suggest that development of therapeutic strategies to influence such microenvironmental cues could be significant in melanoma therapeutics, in terms of both early detection and prevention metastatic invasion.



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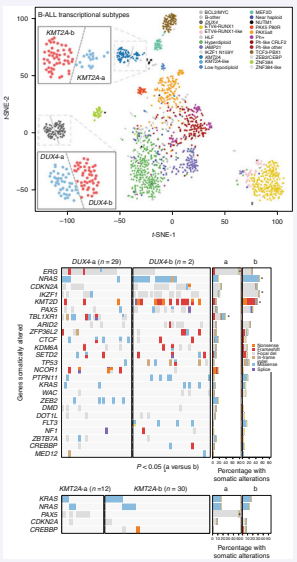
Analysis of the genomic drivers of ALL

Brady et al. performed whole-genome, exome, and transcriptome sequencing of 2754 pediatric patients with acute lymphoblastic leukemia (ALL), the most common childhood cancer. Of the 376 putative cancer driver mutations identified, the group demonstrated that ALL cases harbored a median of four per sample, despite a generally low mutational burden. Most samples harbored at least one rare gene alteration, including driver genes associated with ubiquitination, and SUMOylation. Despite the list being long and the genes often not shared between patients, those identified funneled into key pathways whose alteration feeds either the initiation or perpetuation of the cancer. In hyperdiploid B-ALL, chromosomal gains are acquired early and synchronously before ultraviolet-induced mutation—except in B-ALL cases with intrachromosomal amplification of chromosome 21, where they precede ultraviolet-induced mutation. *DUX4*- and *KMT2A*-rearranged subtypes separate into *CEBPA/FLT3*- or *NFATC4*-expressing subgroups, with potential clinical implications.



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