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MODERN PATHOLOGY

Atypical-to-typical mitoses ratio is prognostic in breast cancer

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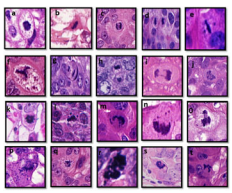

Lashen et al. sought to better understand the clinical significance of atypical mitosis in breast cancer. They started by quantifying atypical and typical mitotic features and correlating them with clinicopathological variables in a large cohort of breast cancer samples. A second set was assessed in The Cancer Genome Atlas (TCGA) breast cancer (BRCA) dataset and linked to genetic alterations and pathways. The median count of typical mitoses was 17 per 3 mm^2 (range, 0–120) while the median count of atypical mitoses was 4 per 3 mm^2 (range, 0–103). Higher counts of atypical mitoses were associated with clinicopathological signs of aggressive tumor behavior and, along with higher atypical-to-typical mitoses ratios, with poor disease-specific survival. Transcriptomic analysis of the TCGA-BRCA cohort based on atypical mitoses identified 2494 differentially expressed genes, including genes involved in chromosomal localization and segregation, centrosome assembly, spindle and microtubule formation, regulation of cell cycle, and DNA repair. Analysis of atypical-to-typical mitoses ratios appears to have prognostic value in breast cancer patients, independent of the overall mitotic count, and can predict response to chemotherapy in triple-negative breast cancer.

Enhancing data from next-generation sequencing by deriving tumor purity

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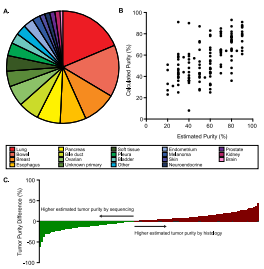

Next-generation sequencing (NGS) data are influenced by tumor purity (defined as the relative contribution of tumor cells compared with all the cells in a pathological specimen), which influences clinical interpretation. Siegmund et al. developed a method for calculating tumor purity using pathologist-guided copy number analysis from sequencing data as a mechanism for taking this influence into account. The group assessed a molecular calculation of tumor purity and showed linear correlation with purity derived from driver *KRAS* or *BRAF* variant allele fractions in colorectal cancers compared with histological estimation in the same data set. They were able to quantitate *ERBB2* copy number in breast cancer with equivocal immunohistochemical staining by calculating tumor purity. They went on to infer germline status of variants in breast and ovarian carcinomas with concurrent germline testing by calculating tumor purity with 100% correct prediction for pathogenic *TP53*, *BRCA1*, and *BRCA2* variants. Accurate tumor purity assessment can help to derive more clinically useful information from existing sequencing data with little additional cost, which offers the potential to expand the utility of cancer NGS and better integrate histopathological and molecular data into patient care.

LABORATORY INVESTIGATION

Assessing Siglec-15 as a novel target for immunotherapeutics

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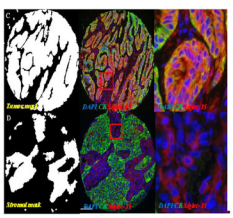

Given the wide-ranging benefits of immune checkpoint blockade in the form of programmed cell death/programmed death-ligand 1 (PD-L1) inhibitors, along with the wide variety of cancer types that do not respond to this blockade, there is a need to seek novel targets for immunotherapy. Shafi et al. assessed the potential of Siglec-15, one such target, across four cancer types. Using quantitative immunofluorescence, the group validated an antibody (QIF) and found increased expression in tumor and immune cells, predominantly in stromal immune cells, across the tumor types. Siglec-15 expression was seen to be mutually exclusive with PD-L1 in all four cancer types, albeit somewhat lower in head and neck squamous cell carcinoma. While acknowledging the need for additional data and the results of the ongoing trial Phase II trial of a humanized

monoclonal antibody to Siglec-15 in non-small-cell lung cancer (NC318), the team proposes that their data support the exploration of additional therapeutics in this area.

Optimization of HER2 expression analysis for improved patient care

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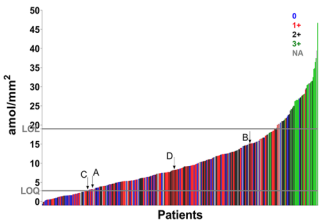

The conventional assay for assessing amplified HER2 from unamplified cases is not sensitive enough to stratify the lower ranges of HER2 expression. With trastuzumab deruxtecan (T-DXd) shown to be efficacious in HER2-low patients with breast cancer, a revision of the assay is needed to optimize patient selection for this and perhaps other applications. Moutafi et al. redesigned the assay to increase resolution and stratify HER2 expression specifically in the unamplified cases using the AQUA™ method of quantitative immunofluorescence, testing a range of antibody concentrations to maximize sensitivity in the lower range of HER2 expression. Using a cell-line microarray with HER2 protein measured by mass spectrometry, they then measured the amount of HER2 protein in units of attomols/mm^2 and determined that low HER2 range expression in unamplified cell lines is 2–20 attomol/mm^2. The group's analysis of 364 breast cancer cases from Yale New Haven Hospital showed that 67% of the population has HER2 expression above the limits of quantification and below those seen in HER2-amplified breast cancer. They propose that their assay could be used to determine the levels of HER2 required for response to T-DXd and similar drugs developed in its class.

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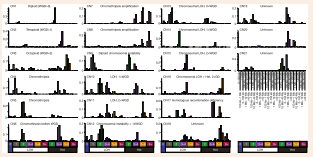
Copy number signatures define cancer genomes

Assessing copy number alterations across samples from The Cancer Genome Atlas (TCGA), Steele et al. generated and tested a conceptual framework to look for patterns in human cancers. A set of 21 copy number signatures were identified that explained the copy number patterns of 97% of samples. The group began by identifying the relationship between their signatures and a variety of cancer types in order to assess their method across a broad range of possibilities. They then challenged their method and their signatures when associated with loss of heterozygosity (LOH). Here they demonstrated that 9 of their 21 signatures were positively correlated with LOH regions and found around known tumor suppressor genes. They observed an enrichment of CN17 in samples that harbored germline and/or somatic mutations in the key HR genes *BRCA1* and *BRCA2*, which they explored further by examining the promoter methylate status of *BRCA1* in breast cancers with CN17 attribution. The signatures were also assessed for association with cancer-driver genes, and a positive association was shown between CN17 and *TP53* mutations in human papilloma virus head and neck squamous cell cancer. The team concluded that their mechanism-agnostic pan-cancer compendium of copy number signatures derived from allele-specific profiles will begin to solidify a nascent field with huge potential for improving our understanding of a wide variety of clinical and biological questions with regard to cancer progression, diagnosis, and treatment.



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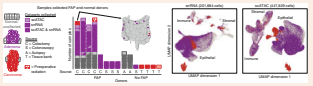
Ascertaining a malignant continuum in colorectal cancer development

Becker et al. performed single-cell analyses to chart the changes that occur during the transition from healthy colon through precancerous adenomas (polyps) toward colorectal cancer (CRC). The group took single-cell transcriptomes from 1,000 to 10,000 cells per sample from 48 polyps, 27 normal tissues, and 6 CRC samples collected from patients with and without germline *APC* mutations. A continuum of epigenetic and transcriptional changes occurs in stem-like cells, found in a large fraction of samples charting the transition. Advanced polyps were shown to have an increased number of stem-like cells, regulatory T cells, and pre-cancer-associated fibroblasts. In addition, gene expression changes could be observed along the malignant continuum, with ten *k*-means clusters corresponding to groups of genes that become differentially expressed during malignant transformation. The consistent changes led the group to question whether similar organized progression continuums may be present in other cancers, along with whether there is any possibility of observing a pathway to metastasis. They believe that their analysis can answer these questions, with overarching implications for prognostic tools in CRC and possibly patients with other types of cancer.



Nature Genetics 2022;54:985–995; https://doi.org/10.1038/s41588-022-01088-x

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