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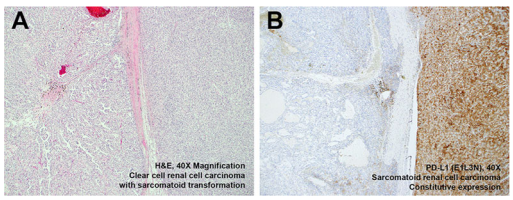
MODERN PATHOLOGY

9p24.1 amplification and PD-L1 expression in renal cell carcinoma

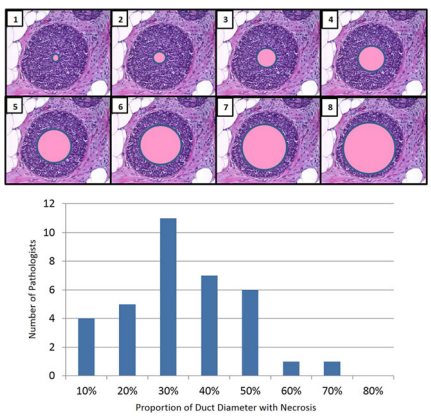
https://doi.org/10.1038/s41379-019-0269-x



Gupta et al. used next-generation sequencing–based copy-number analysis and fluorescence in situ hybridization to assess amplifications in *JAK2*, *PD-L1*, and *PD-L2* at 9p24.1 in renal tumors with amplification at these loci. They found that amplification at these loci was enriched in renal tumors with sarcomatoid transformation with constitutive and intrinsic expression of PD-L1. After interrogating their finding against a "validation cohort" of 398 high-grade renal tumors, they found no prognostic effect and believe that the PD-L1 expression was likely, instead, to be reflective of advanced disease. They therefore propose that additional mechanisms need to be assessed. Two patients with 9p24.1-amplified sarcomatoid renal tumors showed significant response to immunotherapy, which suggests to the authors that such amplification could potentially be a marker for enhanced response to immunotherapy and that screening could inform patient management.

Standardization of histological features in DCIS

https://doi.org/10.1038/s41379-019-0262-4



Variability in observation of pathological findings remains a region for optimization in cancer therapeutics. In the active surveillance of ductal carcinoma in situ (DCIS), the presence of comedo necrosis is an exclusion criterion for many clinical trials; however, the threshold for diagnosis of comedo necrosis is not standardized. Harrison et al. sent standard images with pink circles representing necrosis at 10–80% of the duct diameter to 35 pathologists and asked them to select the image showing the minimum extent of duct diameter required for a diagnosis of comedo necrosis. Of the 35, 4 said 10%, 5 said 20%, 11 said 30%, 7 said 40%, 6 said 50%, and 1 each said 60 and 70%. Even among experienced breast pathologists, the threshold is highly variable. Standardization of histological features with operational criteria is necessary to uniformly qualify patients for participation in active-surveillance clinical trials.

LABORATORY INVESTIGATION

Possible druggable target in TNBC

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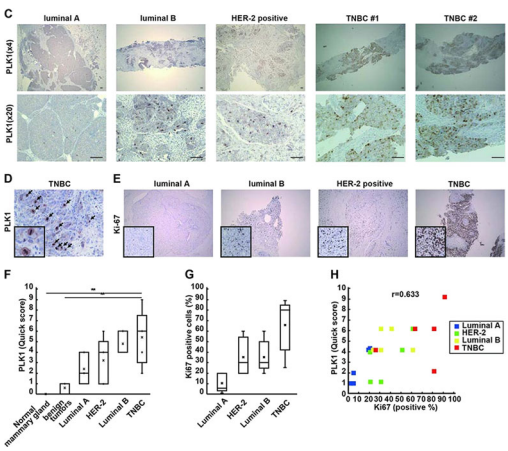

Using an siRNA-mediated knockdown screen, Ueda et al. identified Polo-like kinase (PLK1) as a potential therapeutic target for triple-negative breast cancer (TNBC). Use of either knockdown or a small-molecule inhibitor of PLK1 (BI-2536) induced cell cycle arrest and evoked a polyploid cell population with increased DNA content and nuclear size. The knockdown effects were supported by the fact that PLK1 expression was also shown to be overexpressed in TNBC tissues compared with normal mammary tissue or benign breast tumors. The authors note that phase I human studies have shown BI-2536 to be safe, but its efficacy has not yet been validated in phase II trials. They propose further

in vivo studies to confirm its potential as a therapy in a properly selected TNBC population based on PLK1 expression, potentially identifying a viable target in this challenging breast cancer population.

Protease-mediated availability of HLA binding affects melanoma outcomes

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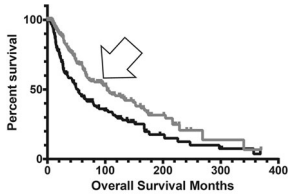
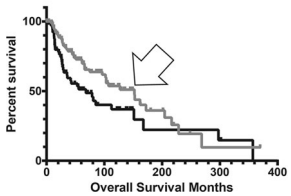


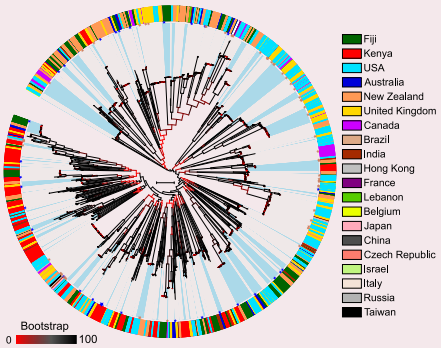


Seeking to better define the role of proteases in the spread and progression of cancers, Zaman et al. established a bioinformatics approach to assessing the impact of mutated proteins on the sensitivity of matrix metalloproteinase-2 (MMP2) in melanoma. Mutant amino acids adjacent to MMP2 sites in cutaneous melanoma were associated with better survival rates and an increased proportion of mutant peptides with high human leukocyte antigen (HLA) class I–binding affinities not seen in the control groups. Bioinformatics analysis indicated that patients with amino acid substitutions due to mutations adjacent to MMP2- and MMP14-sensitive sites had a better overall survival than patients without such mutations. This might also affect response to immune checkpoint blockade since T-cell infiltrates in melanoma varied. The investigators propose that lack of protease-mediated good HLA class I binders may impede the immune response and thus impact treatment choices and patient outcomes.

nature.com/pathology

Broad DNA sequencing yields streptococcal vaccine candidates

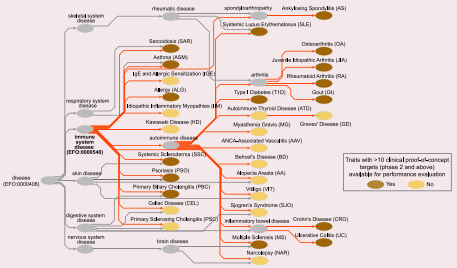
Davies et al. investigated the global genomics of group A *Streptococcus* (GAS; *Streptococcus pyogenes*), a bacterial pathogen for which there is no effective commercial human vaccine. They used high-throughput DNA sequencing to analyze 2083 globally sourced GAS genomes and found widespread genomic heterogeneity driven by homologous recombination with overlaid gene plasticity. Across 22 countries the authors isolated 290 clinically associated genomic phylogroups, demonstrating the challenge of a single global vaccine design. Of 28 vaccine antigen candidates, 15 had both low naturally occurring sequence variation and high coverage across the GAS population. The group modeled the population-based antigenic variation against protein crystal structures to identify functional/structural constraints as well as selection pressure. This platform and these techniques could provide a mechanism for determining vaccine coverage for pathogens.



Nature Genetics 2019;51:1035–1043; https://doi.org/10.1038/s41588-019-0417-8

Genetic approach to drugging immune-related traits

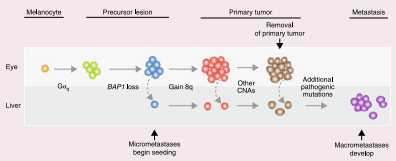
Identification of appropriate targets for drug design is complex. Factors include genetic support and translational use of genome-scale data. There has been statistical failure of candidate drugs in later-stage clinical trials due to lack of efficacy when these targets are not optimally selected. Fang et al. sought to integrate functional genomic and immune-related annotations with network connectivity to optimize target validation for 30 immune traits, developing what the authors call the priority index. The open-access platform, validated by identifying currently used therapeutics, predicts activity from high-throughput screens and prioritizes underexplored targets. The group hopes that it will accelerate early-stage drug target selection for immune-mediated disease by increasing community data collation. If successful, it could de-risk one of the major causes of failure during late-stage clinical trials.



Nature Genetics 2019;51:1082–1091; https://doi.org/10.1038/s41588-019-0456-1

Novel biomarkers of uveal melanoma

Uveal melanoma, which originates from melanocytes in the eye, constitutes less than 5% of invasive melanomas in the United States and has a markedly higher mortality rate than that of other forms of melanoma. Shain et al. used multiregion DNA sequencing of primary uveal melanomas and their matched metastases to identify driver mutations. They discovered novel driver mutations demonstrating that early mutational activation of the Gαq signaling pathway is pathognomonic of uveal melanoma, along with a sequence of events for these mutations undergoing selection. *BAP1* loss was shown in several cases, suggesting that metastatic dissemination may occur before a primary tumor develops a full complement of oncogenic mutations. Some ordering of oncogenic events was also determined. The more extensive cataloging of mutations and selection pressure during progression offers candidate biomarkers for assessing staging and prognosis of uveal melanoma that have not previously been available.



Nature Genetics 2019;51:1123–1130; https://doi.org/10.1038/s41588-019-0440-9