Germline genetics, host immunity and the microenvironment in cancer progression and immunotherapy response

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Abstract

Tumors with the same diagnosis can harbor different molecular profiles and exhibit variable responses to the treatment. When and why these differences arise remains unknown.

Recently, we found that germline variants in key oncogenes influence immune surveillance and tumor development. Interrogating nearly 6,000 breast tumors, we demonstrated that germline-derived epitopes in recurrently amplified genes influence somatic evolution by mediating immunoediting. For example, individuals with high germline-epitope burden in human epidermal growth factor receptor 2 (HER2/ERBB2) are less likely to develop HER2-positive breast cancer compared with other subtypes. The same holds true for recurrent amplicons defining aggressive estrogen receptor (ER)–positive subgroups. Tumors that overcome such immune-mediated negative selection are more aggressive and demonstrate an "immune cold" phenotype. These data indicate a role for the germline genome in dictating somatic evolution and the subtype of disease a patient develops, while uncovering a broad source of clonal antigens.

In tandem, we have sought to understand molecular and microenvironmental determinants of response to immune checkpoint inhibition (ICI). Towards this goal, we analyzed longitudinal tissue samples, including pre- and on-treatment biopsies from metastatic triple negative breast cancer patients enrolled in the TONIC phase II TONIC of induction therapy followed by nivolumab. Through multiplexed imaging of 294 tumors from 117 patients, we quantified the subcellular localization of 37 proteins to identify the location and phenotype of each cell, as well as their spatial distribution, diversity, and functional marker status. Spatial features, including the degree of mixing between cancer and immune cells, the diversity of the neighboring immune cells surrounding cancer cells, and the degree of T cell infiltration at the tumor border were most strongly associated with benefit from ICI. However, non-spatial features, including the ratio between T cell subsets and cancer cells and PD-L1 levels on myeloid cells, were also predictive. Multivariate models predicted ICI benefit at the pre and on-treatment timepoint, with improved performance in the latter. Similar temporal trends were seen in transcriptome data. These findings shed light on the determinants of immunotherapy response with implications for the design of future trials.

Biography

Christina Curtis, PhD is the RZ Cao Professor of Medicine, Genetics, and Biomedical Data Science and Director of AI and Cancer Genomics at Stanford University. Her research has led to new paradigms in understanding how human tumors evolve and metastasize and has redefined the molecular map of breast cancer. Dr. Curtis has been the recipient of multiple awards, including the NIH Director's Pioneer Award and the AACR Award for Outstanding Achievement in Basic Science. She is a Kavli Fellow of the National Academy of Sciences, a Susan G. Komen Scholar, and a Chan Zuckerberg Biohub Investigator. Dr. Curtis serves on the editorial boards of numerous journals, including Science and Cancer Discovery, as an advisor to biotech and biopharma, and as a member of the AACR Board of Directors.