THE NEXT GENERATION OF IMMUNOTHERAPY RESPONSE SIGNATURES REVEALED BY BIOPHYSICAL SIMULATIONS

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Background Although immunotherapy has become standard-of-care for many cancers, the number of benefiting patients remains relatively small. Current markers of response (e.g., PD-L1) have proven only modestly useful for distinguishing IO-responders vs. non-responders. Here, we present a proof-of-concept approach for the rapid, non-invasive assessment of immunotherapy response prediction using biomarker imaging signatures.

Methods We used publicly available datasets (ISPY1 and ISPY2 non-IO-treated patients) to calculate the expression levels of gene signatures across breast cancer subtypes. We analyzed these imaging datasets using TumorScope, a biophysical simulation engine, to identify biomarkers (features) present within IO-responsive tumors. We then correlated this response to biological processes and hallmark cancer gene signatures. TumorScope uses patient standard-of-care data, including high spatiotemporal resolution medical images (e.g., DCE-MRIs) to predict a patient’s probability of achieving a pathological complete response (pCR). Next, we calculated the spatial distribution of these features across tumors. To specifically identify the IO-response signatures, we calculated the feature thresholds associated with pCR in response to IO using the ISPY2 IO-treated patient dataset (linear regression of the training set, n=63). This spatial biomarker-based approach, SimbIOScope, showed comparable predictive power as the traditional biopsy-based transcriptomic approach. We further validated this approach in an independent cohort from a single center (n=12), and applied our method to a large IO-naïve population (n=292) to assess the model’s predictive capability.

Results Spatially-resolved biomarkers of immune evasion in triple negative breast cancer (TNBC) and HR+/HER2- tumors identified individuals with resistance to IO therapy, and had similar predictive power to transcriptomic analysis. We found that baseline (prior to therapy) high levels of immune evasion signatures in IO non-responders are associated with hypoxia (r=0.45, p<1x10^-6) and autophagy in TNBC patients, and with low angiogenesis (r=-0.40, p=0.006) in HR+/HER2-patients. When tested on an independent patient cohort (n=12), SimbIOScope correctly predicted pCR in over 91% of cases. In a larger reference cohort (n=292), SimbIOScope predictions of pCR were consistent with the empirical increase observed in clinical trials. Our analysis predicted a 14% increase in pCR for TNBC tumors above baseline with the addition of the checkpoint inhibitor pembrolizumab, as compared to the 13.6% pCR increase observed in clinical trials (Keynote 522).

Conclusions SimbIOScope imaging biomarkers and analyses efficiently identify the cohort of patients likely to respond to immunotherapy. Its imaging analytic capabilities position SimbIOScope as a critical tool when planning cancer treatment options, and expands IO-response prediction beyond traditional biomarkers.

REFERENCES