Background: Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, accounting for 75% of deaths due to skin cancer, excluding melanoma. Although prognoses are typically favorable, metastasis and resistance to immune checkpoint inhibitors pose an emerging threat. There are few biomarkers that can reliably aid in patient stratification, thus multiplex strategies are required to understand the dynamics of tumor resistance and immune regulation over the course of therapy. Here, we aim to track the tumor microenvironment (TME) dynamics over the course of immune checkpoint inhibitor therapy (ICI).

Methods: Our study investigates the spatial TME landscapes of cSCC tissues from patients over the course of immunotherapy treatment. An ultrahigh-plex antibody panel encompassing cell lineages, activation states, immune checkpoints, structural and metabolic markers was deployed on the PhenoCycler®-Fusion spatial biology platform for analysis of the tissue microenvironment. Deep analysis was performed to identify the cellular phenotypes, spatial neighborhoods and functional states driving tumor pathogenesis and response to immunotherapy.

Results: Our data reveals dynamic changes in the TME phenotype compositions, metabolic states, and spatial signatures over the course of therapy. In patients with resistant disease, metabolic features were observed, specifically within the tumor compartments. Overall, ultrahigh-plex phenotyping of the tumor landscape in cSCC reveals novel insights into the key cellular and molecular determinants of tumor biology and clinical outcome.

Conclusions: Here, using a multiplex spatio-temporal approach with protein-based spatial phenotyping, we interrogated the pathobiology of cSCC to identify novel biomarkers of metastasis and resistance for patient stratification and therapeutic intervention.

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