AMJ
ISSN: 0005-2523

ISSN: 0005-2523

Volume 70, Issue 05, 2025

Spatial Transcriptomic Mapping of the Tumor-Immune Microenvironment in Immunotherapy-Resistant Melanoma Reveals Fibroblast-Mediated T-cell Exclusion

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Abstract

Immune checkpoint inhibitor (ICI) resistance in metastatic melanoma involves complex stromal-immune crosstalk. Utilizing spatial transcriptomics (10x Genomics Visium) and multiplex ion beam imaging (MIBI) of 120 patient biopsies, we identified therapy-resistant tumor regions characterized by collagen-dense extracellular matrix produced by *CXCL12*-expressing cancer-associated fibroblasts (CAFs). These CAFs established physical barriers excluding CD8+ T-cells from tumor nests while recruiting regulatory T-cells through CCL22 secretion. Pharmacological inhibition of lysyl oxidase (LOX) enzymatic activity disrupted collagen crosslinking, restored T-cell infiltration, and resensitized resistant tumors to anti-PD-1 therapy in humanized mouse models. This work elucidates stromal determinants of ICI failure.

Keywords: spatial transcriptomics, tumor microenvironment, cancer-associated fibroblasts, immune checkpoint resistance, melanoma, lysyl oxidase inhibition