

1434

TGF β -DEPENDENT LRRC15⁺ MYOFIBROBLASTS DICTATE THE TUMOR FIBROBLAST SETPOINT TO PROMOTE CANCER IMMUNOTHERAPY RESISTANCE

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Background Single cell transcriptomics has led to the generation of large-scale atlases to understand cellular heterogeneity across both healthy and diseased tissues at the highest resolution. Such atlases have allowed for in silico inferences of fibroblast ontogeny and function, but without in vivo substantiation are limited in their utility to inspire novel fibroblast-directed therapies to improve disease outcome. In cancer, single cell studies identified the emergence of a myofibroblast population, in both mice and humans, uniquely marked by a highly restricted leucine rich repeat containing protein, LRRC15. This cancer-associated myofibroblast population expresses a multitude of extracellular matrix (ECM) associated and immunosuppressive genes. Clinically, high expression of an LRRC15⁺ CAF gene signature in bulk RNAseq data from cancer patients correlated with lack of response to anti-programmed death ligand-1 (aPDL1) checkpoint blockade therapy. It remains unclear if LRRC15⁺ CAFs are the cause of this lack of response, or if they represent a read-out of tumor-intrinsic features driving the association. Also missing are in vivo substantiation of the cellular and molecular signals driving LRRC15⁺ myofibroblast development and the direct impact LRRC15⁺ CAFs have on anti-tumor immunity.

Methods To address these gaps, we paired newly developed preclinical genetic tools in murine tumor models of pancreatic cancer with a large clinical dataset of human stromal cell-sorted expression data from 159 cancer patients across 13 tumor types to understand LRRC15⁺ CAF development and function.

Results In mouse models of pancreatic cancer, we provide in vivo genetic evidence that TGF β 2 signaling in healthy Dermatopontin (DPT)⁺ universal fibroblasts is essential for development of tumor-associated LRRC15⁺ myofibroblasts. Analysis of tumors from 159 patients across 13 indications revealed a conserved axis from universal fibroblasts to LRRC15⁺ myofibroblasts. This axis is the predominant driver of fibroblast lineage diversity in human cancers. Using newly developed Lrrc15-Diphtheria toxin receptor knock-in mice to selectively deplete LRRC15⁺ CAFs, we show loss of this population markedly reduced total tumor fibroblast content and recalibrated the CAF composition towards universal fibroblasts. This, in turn, relieved direct suppression of tumor-infiltrating CD8⁺ T cells to enhance their effector function and significantly augmented tumor regression in response to anti-PDL1 immune checkpoint blockade.

Conclusions Collectively, these findings demonstrate that TGF β -dependent LRRC15⁺ CAFs dictate the tumor-fibroblast setpoint to promote tumor growth, directly suppress CD8⁺ T cell functionality, and limit responsiveness to checkpoint blockade.¹ Development of treatments that restore the homeostatic fibroblast setpoint by diminishing pro-disease LRRC15⁺ myofibroblasts may improve patient survival and response to immunotherapy.

REFERENCE

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