Trends in Cancer

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Spotlight

myCAFs are better than yours: targeting myofibroblasts potentiates immunotherapy

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New findings (Krishnamurty *et al.*) implicate a subset of cancer-associated fibroblasts (CAFs) that express leucine-rich repeat containing 15 (LRRC15) in promoting tumor growth in pancreatic adenocarcinoma (PDAC), by suppressing the antitumor immunity of cytotoxic T cells. Genetic ablation of LRRC15+ CAFs resulted in better response to immune checkpoint blockade, suggesting they may be a novel target for therapy.

Cancer-associated fibroblasts (CAFs) are key players in the tumor microenvironment (TME) of solid tumors. In some cancer types, including pancreatic and breast carcinomas, CAFs are the most abundant stromal cell type and their presence is associated with worse prognosis. CAFs were shown to support tumor progression and metastasis by facilitating angiogenesis, remodeling the extracellular matrix (ECM), and by orchestrating the composition and function of the immune milieu in the TME [1]. Thus, achieving specific and efficient therapeutic targeting of CAFs has been a long-standing goal in cancer research.

In a recent issue of *Nature*, Krishnamurty *et al*. elegantly showed in a mouse model of pancreatic adenocarcinoma (PDAC), that genetic ablation of a CAF subpopulation expressing the leucine-rich repeat containing 15 (LRRC15) protein, attenuated tumor progression by alleviating their immunosuppressive interactions with cytotoxic T cells [2] (Figure 1).

LRRC15$^+$ CAFs were previously identified in studies that used single-cell transcriptomics and were shown to express myofibroblastic gene signatures and to emerge uniquely in perturbed (e.g., wound healing, fibrosis) and cancerous tissues [3,4]. LRRC15$^+$ CAFs express gene signatures associated with ECM remodeling, typical of myofibroblastic CAFs (myCAFs). They were found to be upregulated in breast cancer patients following treatment with immune checkpoint blockade (ICB) therapy and shown to be associated with a poor response to ICB in multiple cancer types [5,6].

To identify the origin of LRRC15$^+$ myofibroblasts, Krishnamurty *et al*. used transgenic mouse models that enable temporal and cell type-specific gene targeting, utilizing dermatopontin (DPT), which they have previously defined as a marker for tissue fibroblasts [3]. Targeting of TGFβ signaling in DPT$^+$ resident fibroblasts revealed that TGFβ drives the emergence of LRRC15$^+$ fibroblasts in PDAC. Bulk RNA-sequencing in human cancers confirmed that high levels of LRRC15 expression in fibroblasts is associated with increased TGFβ and worse survival, linking these two programs also in human disease. Furthermore, the authors demonstrated a tumor-promoting role for LRRC15$^+$ CAFs in mouse models of transplantable PDAC: selective depletion of this CAF subset attenuated tumor growth and also caused a shift of the remaining fibroblast population towards a phenotype similar to that of normal tissue fibroblasts, further modifying the tumor-promoting signals in the stromal microenvironment.

The LRRC15$^+$ myCAF signature was previously associated with worse prognosis and with poor response to anti-PDL1 immunotherapy, but the underlying mechanism was unknown. Krishnamurty *et al*. found that depletion of CD8 T cells reversed the tumor-promoting effect of LRRC15$^+$ CAFs, indicating that their protumorigenic effects may be mediated, at least partially, by direct inhibition of CD8 T cell function. Indeed, depletion of LRRC15$^+$ CAFs resulted in reduced expression of dysfunction markers on CD8 cells, including TIM3, LAG3, and CD39, and enhanced expression of activation markers such as TNF and IFNγ. This could be a direct effect of LRRC15$^+$ CAFs on CD8 T cells, or an indirect effect via activation of Tregs, or recruitment of myeloid-derived suppressor cells (MDSCs), as CAFs were previously implicated in both these immune suppression-promoting tasks [6,7].

Interestingly, the authors defined a pi16$^+$ cluster as 'universal' normal fibroblasts. However, this subset of CAFs exhibited enriched JAK–STAT, NF-κB, and TNF signaling pathways, previously defined as characteristics of inflammatory CAFs (iCAFs) [8]. iCAFs were shown in multiple cancer types to negatively affect antitumor immunity [9] and it would be interesting to compare the immune modulating functions of both fibroblast populations. Finally, combining LRRC15$^+$ CAFs ablation with anti-PDL1 treatment improved the effect of ICB on tumor growth and survival in transplantable murine models of PDAC, suggesting that targeting of LRRC15 may be an attractive novel therapeutic approach. Interestingly, an antibody targeting LRRC15 was previously demonstrated to have robust preclinical efficacy against LRRC15 stromal cells in multiple xenograft mouse models of cancer [4].

The vast heterogeneity and lack of universal markers for CAFs has been a major obstacle in CAF therapeutic targeting. CAFs are highly plastic, arise from multiple origins, and are identified by various markers, depending on cancer type and model system [9]. Col1α, αSMA, PDGFRα, PDPN, FAP, and other markers have been suggested

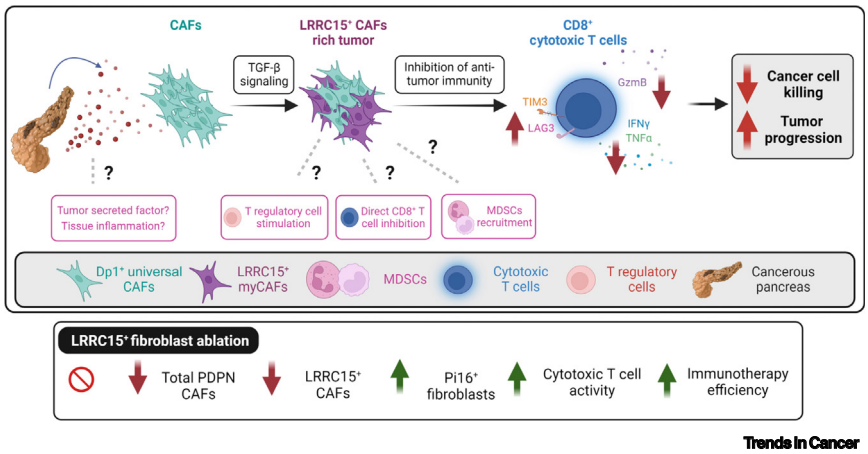

Figure 1. Leucine-rich repeat containing 15 (LRRC15)$^+$ myofibroblastic cancer-associated fibroblasts (myCAFs) impair antitumor immunity. During pancreatic adenocarcinoma (PDAC) progression, enhanced TGFβ signaling in dermatopontin (DPT)$^+$ fibroblasts drives the emergence of a CAF myofibroblast subset that express LRRC15. LRRC15$^+$ myCAFs promote tumor growth and modulate the antitumor functions of cytotoxic T cells in response to immune checkpoint blockade (ICB). Remaining unresolved questions regarding possible mechanisms by which LRRC15$^+$ CAFs mediate immune suppression are indicated by grey dashed lines. Abbreviation: MDSC, myeloid-derived suppressor cell.

to be commonly expressed by CAFs, but it is now clear that none of the above represent a defined and unique CAF subset. For example, αSMA is a marker of myCAFs, but it is also highly expressed by smooth muscle cells and pericytes and across multiple CAF subsets. Indeed, despite high hopes, direct targeting approaches to deplete specific CAF populations, including αSMA$^+$ or FAP$^+$ fibroblasts, yielded unexpected results and/or severe toxicity [10,11] and CAF targeting treatments were thus far unsuccessful in patients.

These disappointments are at least partially because CAF markers are in most cases not specific to CAFs and are highly context dependent. Definitions of CAF subsets may vary according to which organ is investigated, which model was used, how tissue samples were processed, or even which technique was used to profile and characterize CAF populations [9].

Additional points to consider are the different ratios of CAF subsets in different cancer types and their plasticity. CAF subsets most likely represent functional states that may be reversible and possibly interchangeable upon changing of extrinsic microenvironmental cues and thus ablation of a specific subset may result in compensatory expansion of other subpopulations, capable of similar tumor-promoting functions, calling for caution in clinical translation. Thus, it is conceivable that in patients, blocking of tumor-promoting functions of CAFs, based on mechanistic understanding of their cancer type-specific roles, may be a better approach to avoid these hurdles.

These complications highlight the importance of the findings in this study, demonstrating beneficial targeting of a CAF subset in mouse models: LRRC15 was shown to be specific and restricted to myCAFs and, remarkably, no compensatory effect was observed after LRRC15$^+$ myofibroblast ablation in mice with PDAC. Therefore, targeting of LRRC15$^+$ CAFs may be a novel approach to modulate the antitumor functions of cytotoxic T cells in response to ICB. Further analysis of the mechanism and signaling molecules by which LRRC15$^+$ CAFs suppress the function of CD8 T cells will provide molecular tools to better predict patient response to ICB and provide the basis for novel function-based CAF targeted therapeutics.

Declaration of interests

No interests are declared.

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https://doi.org/10.1016/j.trecan.2022.11.001

References

1. Sahai, E. *et al.* (2020) A framework for advancing our understanding of cancer-associated fibroblasts. *Nat. Rev. Cancer* 20, 174–186
2. Krishnamurty, A.T. *et al.* (2022) LRRC15(+) myofibroblasts dictate the stromal setpoint to suppress tumour immunity. *Nature* 611, 148–154
3. Buechler, M.B. *et al.* (2021) Cross-tissue organization of the fibroblast lineage. *Nature* 593, 575–579
4. Purcell, J.W. *et al.* (2018) LRRC15 is a novel mesenchymal protein and stromal target for antibody-drug conjugates. *Cancer Res.* 78, 4059–4072
5. Dominguez, C.X. *et al.* (2020) Single-cell RNA sequencing reveals stromal evolution into LRRC15(+) myofibroblasts as a determinant of patient response to cancer immunotherapy. *Cancer Discov.* 10, 232–253
6. Kieffer, Y. *et al.* (2020) Single-cell analysis reveals fibroblast clusters linked to immunotherapy resistance in cancer. *Cancer Discov.* 10, 1330–1351
7. Monteran, L. *et al.* (2022) Chemotherapy-induced complement signaling modulates immunosuppression and metastatic relapse in breast cancer. *Nat. Commun.* 13, 5797
8. Elyada, E. *et al.* (2019) Cross-species single-cell analysis of pancreatic ductal adenocarcinoma reveals antigen-presenting cancer-associated fibroblasts. *Cancer Discov.* 9, 1102–1123
9. Lavie, D. *et al.* (2022) Cancer-associated fibroblasts in the single-cell era. *Nat. Cancer* 3, 793–807
10. Chen, Y. *et al.* (2021) Type I collagen deletion in alphaSMA(+) myofibroblasts augments immune suppression and accelerates progression of pancreatic cancer. *Cancer Cell* 39, 548–565
11. Saw, P.E. *et al.* (2022) Targeting CAFs to overcome anticancer therapeutic resistance. *Trends Cancer* 8, 527–555