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**CAF-macrophage crosstalk in tumour microenvironments governs the response to immune checkpoint blockade in gastric cancer peritoneal metastases**

*Li Y, Zheng Y, Huang J, et al. CAF-macrophage crosstalk in tumour microenvironments governs the response to immune checkpoint blockade in gastric cancer peritoneal metastases. Gut 2025; 74(3):350-363. doi: 10.1136/gutjnl-2024-333617.*

Gastric cancer peritoneal metastases (GCPM) are notoriously difficult to treat, with poor long-term survival and have a grave impact on the patients quality of life. Although immune checkpoint blockade (ICB) therapies have recently shown promise, identifying which patients benefit most and overcoming resistance remain key challenges. This study sought to characterise the GCPM tumour microenvironment (TME) at single-cell resolution, revealing mechanisms of ICB response and resistance.

Li et al., conducted a phase II trial where patients with GCPM received Sintilimab (an ICB therapy) alongside chemotherapy. Samples from primary tumours, metastatic lesions and peripheral blood underwent single-cell RNA sequencing. This approach provided a high-resolution map of the TME, enabling the identification of key cellular interactions that either support or hinder immunotherapy effectiveness.

Analyses revealed a distinctive TME in GCPM, dominated by immunosuppressive macrophages (SPP1 (Secreted Phosphoprotein 1)+ tumour-associated macrophages) and specialised fibroblasts (THBS2 (Platelet-derived protein thrombospondin-2)+ matrix cancer-associated fibroblasts). These two cell populations interact via a complement pathway (C3 (complement 3)–C3AR1 (complement component 3a receptor 1)) that fosters tumour growth and dampens the immune response. Blocking this pathway in preclinical models reduced the recruitment of immunosuppressive macrophages and enhanced ICB efficacy. Additionally, a subset of natural killer T cells (NKT) (KLRD1 (Killer Cell Lectin Like Receptor D1)+ NKT) expanded in patients who responded to treatment, highlighting their potential role in effective tumour clearance.

A high-resolution single-cell analysis demonstrated that a stroma-myeloid niche—driven by THBS2+ mCAFs (matrix cancer-associated fibroblasts) and SPP1+ TAMs—is a central source of ICB resistance in GCPM. Targeting the complement C3-C3AR1 pathway to disrupt these pro-tumour interactions in vivo seems to significantly enhance immunotherapy outcomes. These findings provide new insights into the specialised TME underlying the immunotherapy resistance of GCPM and practical targets for drug discovery to potentiate ICB therapy.