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COLORECTAL CANCER

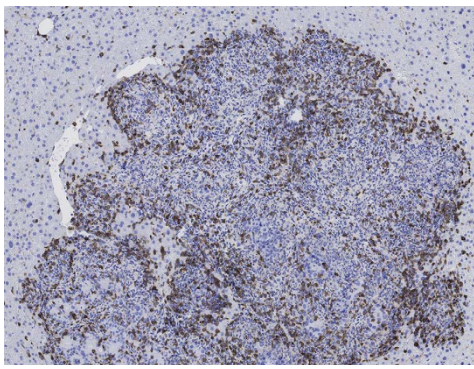
Evading the immune response in metastasis

New research published in *Nature* demonstrates a key role for transforming growth factor β (TGFβ) in driving immune evasion during colorectal cancer (CRC) metastasis in mouse models. Crucially, a combination of TGFβ with an immune checkpoint inhibitor promoted a strong cytotoxic immune response against liver tumours metastasized from CRC in mice, indicating dual immunotherapy as a potential therapeutic approach in advanced CRC.

Key features of the tumour microenvironment (such as lack of T cell infiltration and increased TGFβ levels) have been shown to predict adverse outcomes in patients with CRC. For TGFβ in particular, previous work has shown that tumoral TGFβ levels are associated with a high risk of relapse after CRC treatment, and that some poor prognosis CRC molecular subtypes (microsatellite-stable (MSS) CRC) are characterized by a TGFβ-activated tumour microenvironment. Eduard Batlle and colleagues wanted to explore the interplay between genetic alterations and tumour microenvironment in CRC and during metastasis. In doing so, they developed a mouse model bearing conditional alleles of four main human CRC mutations in intestinal stem cells, which they could then use to create a biobank of mouse tumour organoids for further testing and analysis.

"Reaching the stage of four compounded CRC mutations in one mouse (triggered in adult intestinal stem cells) took 3–4 years of crossing," explains Daniele Tauriello. "These mice allowed us for the first time to observe tumorigenesis from normal mucosa to invasive adenocarcinomas with high metastatic potential," he adds. "Very satisfyingly, mice in this model presented with all the relevant aspects not just of human CRC in general, but of poor prognosis MSS CRC."

In their work, the researchers found that the quadruple-mutant mice developed metastatic intestinal tumours matching key characteristics of MSS CRC, including TGFβ-activated stroma and T cell exclusion. Moreover, immune checkpoint inhibition using an anti-PD-L1 (programmed cell death ligand 1) antibody had only a modest effect in this model. Importantly, inhibition of TGFβ signalling in the tumour microenvironment of the quadruple-mutant mice using the TGFBR1-specific inhibitor galunisertib led to a potent anti-tumour cytotoxic T cell response, preventing metastasis. Finally, dual immunotherapy with galunisertib and an anti-PD-L1 antibody resolved established liver metastases in the CRC mouse model with overt metastatic disease, eradicating most metastases and prolonging recurrence-free survival for over a year and demonstrating that TGFβ signalling in the tumour microenvironment contributes to checkpoint inhibitor failure.



Courtesy of D. Tauriello and E. Batlle, IRB Barcelona.

"A big question is how some CRCs develop a TGFβ-activated microenvironment where others do not, as this seems to be a key (if not the main) distinction between a good or a bad prognosis," says Tauriello, adding that the researchers hope to develop specific models for disease recurrence and to explore immune exclusion in the hope to better understand the underlying mechanisms.

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ORIGINAL ARTICLE Tauriello, D. V. F. *et al.* TGFβ drives immune evasion in genetically reconstituted colon cancer metastasis. *Nature* https://doi.org/10.1038/nature25492 (2018)