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IMMUNOTHERAPY

Inhibition of TGF β enhances immune-checkpoint blockade

Two articles describing how tumour stromal-derived TGF β restrains antitumour immunity have now been published in *Nature*. Both pre-clinical studies present inhibition of TGF β signalling in combination with immune-checkpoint blockade as a potential therapeutic option.

In the first study, Sanjeev Mariathasan and collaborators aimed to identify reliable biomarkers of responsiveness to the anti-PD-L1 antibody atezolizumab in patients with metastatic urothelial carcinoma. The tumours of patients who did not respond to this therapy exhibited an ‘immune-excluded’ phenotype, in which CD8⁺ effector T cells are located in the peripheral stroma of the tumour rather than within the tumour bulk. “By digging deeper into tumour biology in these patients, we discovered upregulation of a gene signature associated with the response of fibroblasts to TGF β signalling,” explains Mariathasan.

Their subsequent experiments were carried out in a mouse model of mammary carcinoma that exhibits the immune-excluded phenotype. In these mice, the combination of anti-PD-L1 and anti-TGF β antibodies resulted in improved antitumour activity. “In this model, TGF β signalling restricts the presence of T cells to the tumour-associated stroma and, thus, dual blockade of this pathway and PD-1/PD-L1 signalling enables T cell migration into the tumour,” adds Mariathasan.

In the second study, Daniele Tauriello and colleagues developed a mouse model combining the four

pathways commonly mutated in human colorectal cancer (CRC). “None of these alterations have been linked to metastasis, which instead depends on the tumour microenvironment. To our surprise, a high proportion of mice combining all mutations spontaneously developed liver or lung metastasis. These mice presented with all the relevant aspects of poor prognosis, microsatellite-stable CRC, including stromal TGF β activation and T cell exclusion, among others,” Tauriello describes. In these mice, treatment with the inhibitor of TGF β signalling galunisertib elicited an antitumour immune response, which prevented metastasis. “Successful liver metastasis relied on TGF β to abrogate T cell infiltration. However, once the metastases grew past a certain stage, galunisertib monotherapy ceased to be effective,” Tauriello states. When galunisertib and anti-PD-L1 were given in combination, established liver metastases were cured in the majority of mutant mice.

In summary, preclinical studies of advanced-stage urothelial carcinoma and CRC implicate TGF β as a tumour microenvironmental promoter of immune evasion. Clinical studies exploiting this crosstalk mechanism could unveil new strategies to improve the efficacy of immune-checkpoint blockade.

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ORIGINAL ARTICLES Mariathasan, S. *et al.* TGF β attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature* **554**, 544–548 (2018) | Tauriello, D. V. F. *et al.* TGF β drives immune evasion in genetically reconstituted colon cancer metastasis. *Nature* **554**, 538–543 (2018)