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IMMUNOTHERAPY

Macrophages hijack anti-PD-1 therapy

Anti-PD-1 antibodies (αPD-1) can provide long-term clinical benefit, but only for a minority of patients with cancer; our understanding of the mechanisms of response or resistance to these agents is limited. Mikael Pittet and co-workers sought to address this knowledge gap by studying the pharmacokinetics and pharmacodynamics of αPD-1 within the complex tumour microenvironment.

Intravital microscopy was used to investigate, in real-time and at subcellular resolution, the interactions between αPD-1 and $CD8^+$ T cells (which express PD-1), tumour-associated macrophages (TAMs), and tumour cells in a mouse model of cancer. Commenting on the major findings, Pittet explains: "binding of αPD-1 to T cells within tumours occurs soon after infusion, as expected, but αPD-1 are transferred from T cells to TAMs within only a few minutes." Notably, evidence indicated that TAMs physically remove the antibodies from the surface of T cells, although phagocytosis was ruled out as the main mechanism of antibody sequestration. Instead, "αPD-1 uptake by TAMs depends both on the Fc domain of the antibody, particularly its glycosylation, and on Fcγ receptors (FcγRs) expressed by TAMs," Pittet adds. These findings were recapitulated using primary human immune cells and an approved αPD-1, nivolumab, *in vitro*.

Importantly, interactions of αPD-1 with TAMs seem to contribute to drug resistance because antibody-mediated blockade of FcγRs enhanced the efficacy of αPD-1 therapy in mice; specifically, no nonresponders were seen with combined treatment, contrary to observations in mice treated with αPD-1 alone.

Together, these findings indicate that preventing TAMs from 'hijacking' αPD-1 might prolong the pharmacological engagement of antitumour T cells, thereby increasing the effectiveness of therapy. Pittet concludes, "this could potentially be achieved by modifying αPD-1 via Fc engineering or glycan modification, by blocking FcγRs, or by targeting macrophages or other cells that express FcγRs.

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ORIGINAL ARTICLE Arlauckas, S. P. *et al. In vivo* imaging reveals a tumor-associated macrophage-mediated resistance pathway in anti-PD-1 therapy. *Sci. Transl Med.* **9**, eaal3604 (2017)