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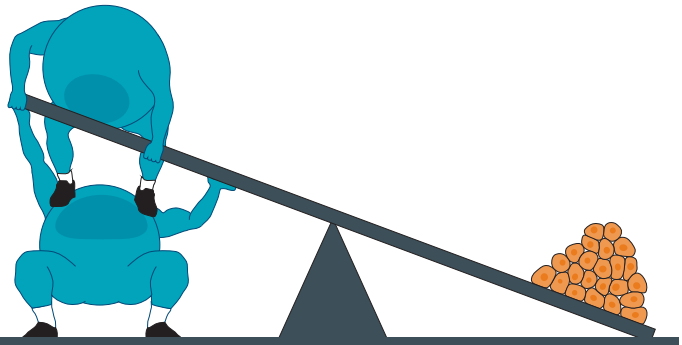

IMMUNOTHERAPY

Reinvigorated T-cell numbers counterbalance tumour burden

Blockade of the programmed cell death protein 1 (PD-1) immune checkpoint has defined a new era of anticancer therapy. However, only a minority of patients respond to PD-1 blockade, and reliable predictive biomarkers have proved elusive. In a recently published study, researchers have identified a blood-based biomarker that provides early insight into the likely therapeutic success or failure.

One of these researchers, Tara Gangadhar, comments on the rationale for their study: "we previously observed an inverse association between tumour burden and a clinical response to PD-1 blockade, but with no clearly defined relationship or mechanism. We had also observed markers of T-cell activation in the blood of most patients, but tumour shrinkage only in a minority. Thus, we hypothesized that immune activation relative to tumour burden determines responses."

To test this hypothesis, immune profiling was performed using peripheral blood taken from 29 patients with metastatic melanoma before and every 3 weeks after treatment with the anti-PD-1 antibody pembrolizumab. Expansion of populations of PD-1$^+$ T cells — particularly exhausted T cells — positive for the proliferation marker Ki67, indicating reinvigoration of these cells, was identified as a key pharmacodynamic indicator of a response to PD-1 blockade.

Of note, this immunological effect was observed in 74% of the patients, peaking at around weeks 3–6 and declining thereafter, but the clinical response rate was only 38%. As hypothesized, "the therapeutic failure in many patients could be predicted not by the immune rejuvenation alone, but by the ratio of immune reinvigoration to tumour burden," states John Wherry, who was also involved in the study. In particular, a PD-1$^+$Ki67$^+$ T cell:tumour burden ratio of >1.94 at week 6 was associated with a favourable response rate and survival; this 'reinvigoration score' threshold was validated in a separate cohort of 18 patients.

These findings have important implications for therapy: not only could this ratio be used to identify responders very early in the course of treatment, but the degree of T-cell reinvigoration in relation to tumour burden might also guide the use of novel 'next-generation' immunotherapies in future studies. "Patients with moderate reinvigoration, but a large tumour burden might be good candidates for additional blockade of other immune checkpoints to help further boost immune reinvigoration," Wherry explains. "By contrast, patients with no or very low immune reinvigoration, regardless of tumour burden, might need some form of vaccination (vaccine, radiotherapy, oncolytic virus) to kick-start the immune response." Importantly, as the immune response occurs very rapidly and transiently, any co-therapy should probably be applied early during treatment.

Wherry concludes, "we hope to enhance the utility of blood-based immune monitoring, to not only chart the clinical course of individual patients, but also to identify novel mechanisms of treatment success and failure."

David Killock

ORIGINAL ARTICLE Huang, A. C. *et al.* T-cell invigoration to tumour burder ratio associated with anti-PD-1 response. *Nature* http://dx.doi.org/10.1038/nature22079 (2017)