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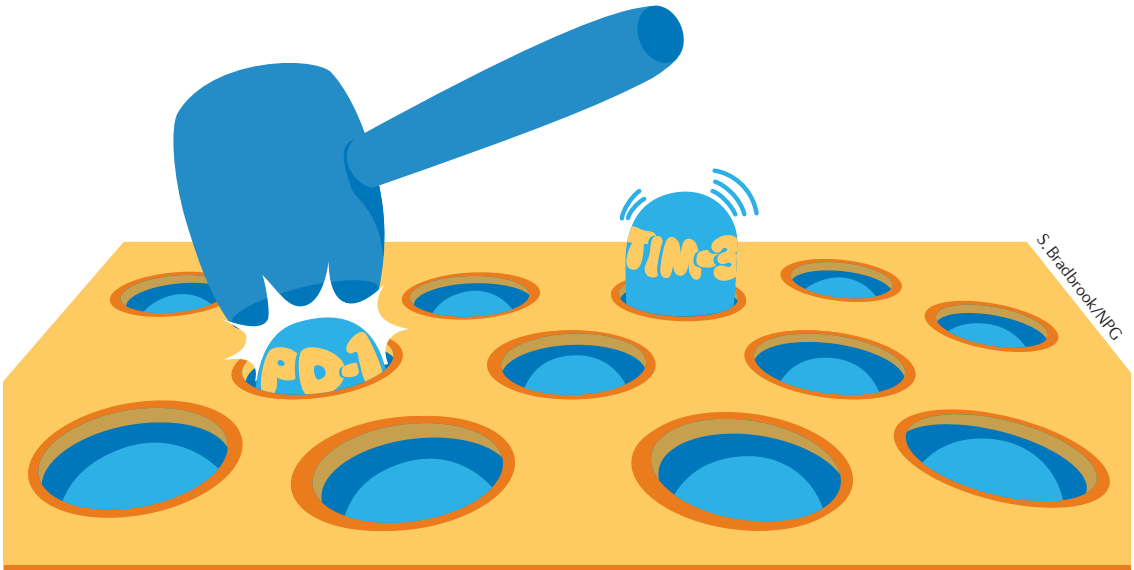

IMMUNOTHERAPY

PD-1 says goodbye, TIM-3 says hello

Immune-checkpoint inhibitors, notably antibodies targeting the PD-1/PD-L1 axis, have demonstrated efficacy as therapeutic agents for several tumour types. As Peter Hammerman explains, however, "little is known about which patients are likely to respond to these agents and, if they respond, the possible mechanisms of resistance to therapy are unknown." Findings now published by Hammerman and colleagues show that TIM-3 and other immune checkpoints are upregulated as a result of adaptative resistance.

In the first part of this study, the investigators used two genetic models of lung cancer driven by mutations in genes that are clinically relevant to this malignancy, such as *EGFR* and *KRAS*, in fully immunocompetent mice. The tumour immune microenvironment was analysed before, during and after treatment with a PD-1-blocking antibody. The expression of several immune checkpoints — most notably, TIM-3 — was upregulated in T cells from animals that developed resistance to the anti-PD-1 treatment. In independent experiments, resistance to anti-PD-1 therapy was prevented when an anti-TIM-3 antibody was administered together with an anti-PD-1 agent.

Importantly, the authors undertook validation studies using samples derived from two patients with lung adenocarcinoma who had developed progressive disease after receiving anti-PD-1 therapy. The immune cells present in effusion samples collected from these patients were analysed, and their phenotypic profile was compared with that of immune cells from five patients with non-small-cell lung cancer who had not received anti-PD-1 treatment; higher levels of TIM-3, but not of other immune markers, were detected in T cells from the patients who had developed resistance to anti-PD-1 therapy compared with the other patients.

These results indicate that, in the setting of anti-PD-1 therapy, treatment failure is associated with upregulation of alternative immune checkpoints that act to limit the antitumour immune response. Hammerman indicates, "this mechanism had been demonstrated in the infectious disease literature, but this is the first report in a cancer context". Future studies need to address how the immune response can be monitored during treatment in order to identify novel approaches to potentiate the effect of PD-1/PD-L1 blockade. As Hammerman notes, "responses to PD-1/PD-L1 therapy remain suboptimal in the majority of patients and there is much to learn and improve on."

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ORIGINAL ARTICLE Koyama, S. *et al.* Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. *Nat. Commun.* http://dx.doi.org/10.1038/ncomms10501 (2016)