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The dark side of PD-1 receptor inhibition

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Abstract

Inhibiting the protein PD-1 can activate T cells that trigger immune responses against tumour cells. But it emerges that, in mice, this immunotherapy exacerbates a cancer that involves the T cells themselves.

Cancer therapy has been revolutionized by drugs that enhance the activation of immune cells called T cells, which can directly recognize and eliminate damaged or cancerous cells in the body. Administration of such drugs prompts the patient's own immune system to fight tumours. But what happens if the cancerous cells are the T cells themselves? Wartewig *et al.* [1] report on page 121 that a widely used cancer immunotherapy actively promotes tumour progression in a mouse model of a cancer called T-cell non-Hodgkin's lymphoma (T-NHL).

T-cell hyperactivation during chronic exposures to pathogens can damage surrounding healthy tissues. To protect the body from this phenomenon, T cells express the receptor protein known as programmed cell death-1 (PD-1) on their surfaces[2]. When PD-1 is bound by its ligand, PD-1 signalling is activated. This inhibits T-cell-receptor signalling, attenuating downstream signalling through the PI3K and PKCθ pathways[2,3] and so rendering the T cell inactive and non-proliferative. But this protective mechanism can also be co-opted by tumour cells, which often express PD-1 ligands on their surfaces that enable them to prevent T-cell responses and escape destruction. Reactivating T cells to act against tumours using an antibody that blocks ligand binding to PD-1 has become an integral part of therapy for several cancers (Fig. 1a).

During an investigation of the mechanisms underlying T-NHL, Wartewig *et al.* uncovered a previously unknown role for PD-1 in T-cell cancers. The authors made use of a mouse model of T-NHL in which a subset of T cells are engineered to express a cancerous protein that drives human T-NHL. These T cells proliferate continuously, leading to cancer. By using a genetic screen to introduce random mutations into the animals' T cells, the researchers

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found that interfering with PD-1 expression reliably induced massive proliferation of cancerous T cells. Moreover, in humans, mutations in the gene encoding PD-1 correlated with more-aggressive lymphoma.

This makes sense, because in T-NHL, the T cells are the tumour cells. Inactivation of T cells through PD-1 signalling does not protect the tumour — as would normally be the case — but rather suppresses proliferation of cancerous cells (Fig. 1b). Thus, T-cell tumours such as T-NHL can benefit from the loss of PD-1 signalling. The source of the PD-1 ligand that activates PD-1 signalling in T-NHL could be any of a range of immune-cell types, or even the tumour cells themselves.

Finally, Wartewig *et al.* showed that treatment of the T-NHL model mice with a PD-1 antibody, as would be done for patients, led to rapid and lethal proliferation of the cancerous T cells. This highlights a dangerous possible side effect of using anti-PD-1 treatment in the clinic.

Anti-PD-1 treatment significantly improves survival rates associated with therapies for several types of solid tumour, including skin[4] and lung[5] cancers. It has also proved beneficial in blood cancers that are not T-cell derived[6]. But Wartewig and colleagues' work indicates that the treatment might actually worsen certain cancers. The authors suggest that, in humans who have PD-1 mutations, the use of PI3K inhibitors might be preferable to treatment with an anti-PD-1 antibody.

How should these findings be interpreted in the context of human cancer? First, it is necessary to consider that the T-cell population is diverse and contains several subsets of cells that have distinct functions and characteristics. A study[7] recently showed that PD-1 blockade activates specific T-cell subsets, rather than having a general effect on the entire population. This suggests that anti-PD-1 treatment might aggravate disease progression only if it induces proliferation of the specific T-cell subtype that yielded the cancer.

Second, PD-1 inhibition also affects other types of cell in the cancer milieu — for instance, immune cells known as macrophages that 'swallow' damaged cells, disposing of them through a process called phagocytosis. In a tumour setting, macrophages do not necessarily eliminate tumour cells; instead they can promote tumour growth. PD-1 is expressed on tumour-associated macrophages, and PD-1 signalling reduces phagocytosis[8]. Moreover, anti-PD-1 treatment restores phagocytosis in tumour-related macrophages and reduces tumour burden[8]. These data indicate that macrophages should be considered when analysing the effects of PD-1 blockade on cancer.

PD-1 blockade has previously been used in patients with T-cell lymphoma without yielding disastrous results[9], highlighting the need to uncover the other mechanisms at play. Perhaps PD-1 blockade activates other types of cell that combat the tumour, or maybe it did not affect the cancerous T-cell subtype in these patients.

In the era of immune-based cancer therapies, Wartewig and colleagues' study raises an important point: drugs that stimulate T-cell activity should be carefully studied to ensure that their use doesn't trigger the proliferation of cancerous cells. A better grasp of the detailed

mechanisms that underlie the effects of PD-1 blockade in T-cell-derived tumours is still needed. An understanding of which cells are specifically affected by PD-1 blockade, and what abnormal traits they acquire following treatment, would enable an assessment of the efficacy of using PD-1 blockade to treat specific types of T-NHL. This knowledge should improve the treatments offered in the clinic and reduce possible harmful side effects.

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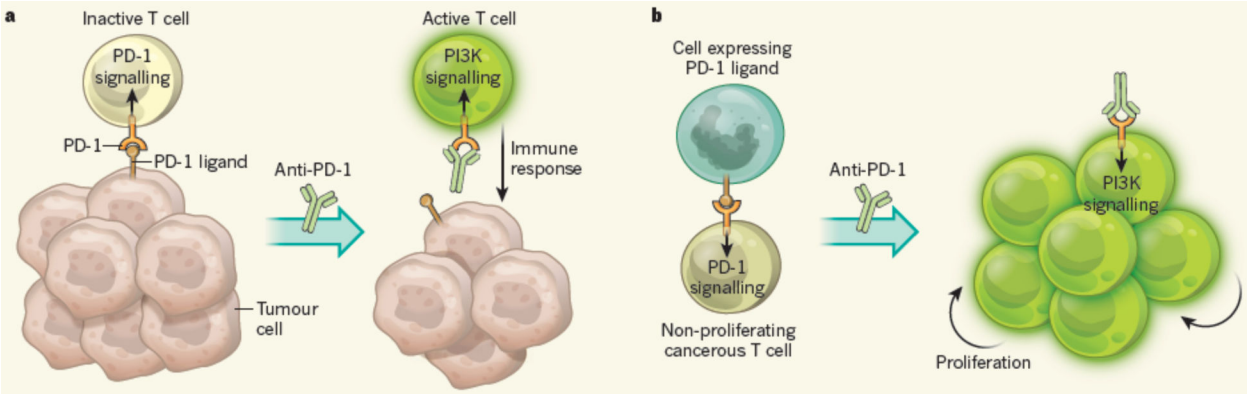

Figure 1|. Dual roles for the PD-1 receptor protein.

a, PD-1 is expressed on the surface of immune cells called T cells. When PD-1 is bound by a ligand produced by tumour cells, PD-1 signalling renders the T cell inactive, preventing immune responses that would destroy the tumour. Treatment with an antibody to PD-1 blocks ligand binding and so PD-1 signalling, instead promoting the PI3K signalling pathway, which is involved in T-cell activation. As such, anti-PD-1 treatment triggers an immune response, **b**, Wartewig *et al.* [1] have demonstrated that PD-1 signalling in a mouse model of T cell non-Hodgkin's lymphoma prevents proliferation of cancerous T cells (the source of the PD-1 ligand was not defined). In these mice, anti-PD-1 treatment can aggravate disease by reactivating the cancerous cells to enable their continuous proliferation.