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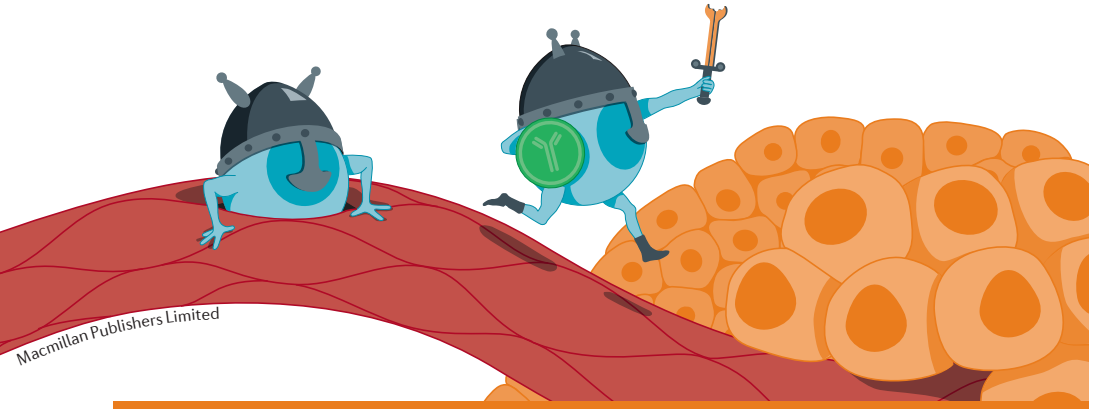

IMMUNOTHERAPY

Combine and conquer — antiangiogenic immunotherapy

The benefits of antiangiogenic therapies for patients with cancer are, arguably, limited. In particular, agents targeting the VEGF pathway are approved only in combination with other therapies, and provide a modest, if any, overall survival benefit. By contrast, antibodies that block the PD-1–PD-L1 immune checkpoint are associated with drastic overall survival improvements, but in only a minority of patients. Restricted T-cell recruitment into tumours, potentially owing to the dysfunctional tumour vasculature, might limit the effectiveness of immune-checkpoint blockade, whereas the activity of anti-VEGF therapy is partially attributed to T-cell infiltration. Thus, the rationale for combining antiangiogenic and anti-PD-1/PD-L1 agents is strong, and is further strengthened by new evidence from two studies published in *Science Translational Medicine*.

In the first study, antiangiogenic therapy with A2V, a bispecific antibody targeting not only VEGF, but also angiopoietin-2 (ANG-2) was associated with survival benefits and suppression of spontaneous metastasis in mouse models of various malignancies. "A key finding was that blocking both ANG-2 and VEGF had superior stimulatory effects on antitumour immunity, as compared with blocking either factor alone," states Michele De Palma, who led the study. Mechanistically, A2V promoted antigen presentation as well as T-cell extravasation, perivascular accumulation, and activation, at least in part, by enhancing vascular normalization. "Another interesting observation was that, despite potently inhibiting tumour angiogenesis and stimulating antitumour immunity, A2V triggered an immunosuppressive response involving the induction of PD-L1 in the remaining tumour blood vessels." This feedback response was mediated by IFNγ released by perivascular T cells, and could be counteracted by PD-1 blockade. De Palma opines: "such combination therapy should be tested in patients with 'cold tumours' that contain too few T cells to respond to checkpoint blockade."

In the second study, researchers sought to investigate the mechanisms of resistance to VEGF pathway inhibitors. They similarly demonstrated that intratumoural T-cell accumulation and activation increased during blockade of either VEGF or VEGFR2, with resultant IFNγ-mediated upregulation of PD-L1 leading to disease relapse. Again, this response could be abrogated, and outcomes improved, by dual blockade of the VEGF and PD-L1 pathways. Of note, the degree of T-cell activation, the level of PD-L1 upregulation, and the efficacy of dual therapy were all correlated, and were all negligible in a model of glioblastoma that is intrinsically resistant to antiangiogenic therapy.

> "…PD-1/PD-L1 blockade can sensitize tumours to antiangiogenic therapy and increase its efficacy, and vice versa"

Notably, PD-L1 blockade enhanced vascular normalization, prolonging the angiostatic effects of VEGFR2 inhibition. In addition, "we found that successful treatment with a combination of anti-VEGFR2 and anti-PD-L1 antibodies depended on the induction of high endothelial venules (HEVs)," explains Gabriele Bergers, who led this study. "The therapeutic induction of HEV hotspots promoted lymphocyte infiltration and activity (generating tertiary lymphoid structures), in part through activation of lymphotoxin β receptor (LTβR) signalling in endothelial cells." Importantly, resistant tumours, including the aforementioned glioblastomas, could be sensitized to 'antiangiogenic immunotherapy' by adding an antibody that activated the LTβR and generated HEVs. "The ability to induce HEVs in tumours would promote T-cell infiltration and might improve — or even sensitize tumours to — anticancer therapy; such an approach would have broad clinical applicability," says Bergers.

Interestingly, the findings of these studies are broadly in keeping with those of a third study, recently published in *Nature*, in which a mutual regulatory loop between vascular normalization and $CD4^+$ T-cell activation was identified, which could be potentiated by immune-checkpoint blockade. Bergers summarizes, "together, these preclinical studies provide evidence that PD-1/PD-L1 blockade can sensitize tumours to antiangiogenic therapy and increase its efficacy, and vice versa."

David Killock

ORIGINAL ARTICLES Schmittnaegel, M. *et al.* Dual angiopoietin-2 and VEGFA inhibition elicits antitumor immunity that is enhanced by PD-1 checkpoint blockade. *Sci. Transl Med.* **9**, eaak9670 (2017) | Allen, E. *et al.* Combined antiangiogenic and anti-PD-L1 therapy stimulates tumor immunity through HEV formation. *Sci. Transl Med.* **9**, eaak9679 (2017) | Tian, L. *et al.* Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming. *Nature* **544**, 250–254 (2017)