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TUMOUR IMMUNOLOGY

Platelets — a new target in cancer immunotherapy?

> platelets can suppress T cell responses against tumours

Although best recognized for their roles in haemostasis, platelets contribute to other biological processes, including immune regulation. Reporting in *Science Immunology*, Rachidi *et al.* show that platelets can suppress T cell responses against tumours through their production and activation of immunosuppressive factors.

Thrombocytosis is linked to poor clinical outcomes in cancer, and Rachidi *et al.* postulated that this could be linked to platelet-mediated immunosuppression. To explore this idea, they compared T cell responses against melanomas established in wild-type mice or in mice with a megakaryocyte-specific deletion of *Hsp90b1*, which have significantly lower platelet counts. Tumour growth was comparable between these two groups in the absence of adoptive T cell therapy (ACT), but following the transfer of melanoma-specific $CD8^+$ T cells (PMEL cells), the platelet-deficient mice had significantly reduced tumour burdens compared with the wild-type mice.

The above finding suggested that platelets may limit the efficacy of T cell-mediated cancer immunotherapy and the authors next explored the mechanistic basis of this. They found that soluble factors (but not platelet microvesicles) from thrombin-activated platelets blocked $CD8^+$ T cell proliferation and interferon-γ production *in vitro*, but had no direct effect on the proliferation of fibroblasts or melanoma cells. Furthermore, treatment of PMEL cells with supernatant from activated platelets before ACT reduced their antitumour activity against melanoma. In supernatants from thrombin-activated human platelets, the authors identified two major fractions with T cell-suppressive activity: the larger fraction (>150 kDa in size) was found to correspond to a complex comprising mature transforming growth factor-β, latency-associated peptide, LTGFβ-binding protein 1 and thrombospondin 1 (TGFβ–LAP–LTBP1–TSP1), whereas the smaller fraction (<1 kDa in size) was dominated by the metabolite lactate. Notably, combined blockade of TGFβ and lactic acid in the supernatant from activated platelets almost completely abolished its T cell-suppressive effects.

Further experiments showed that TGFβ, but not lactic acid, was able to suppress the priming of PMEL cells, so the authors chose to focus on how platelets regulate TGFβ levels. Antibody-mediated depletion of platelets in mice led to a complete loss of active and total TGFβ in serum, but the levels of TGFβ returned to normal as platelet counts recovered. The authors next explored the efficacy of ACT in melanomas induced in mice with either a platelet-restricted deficiency of TGFβ1 or a platelet-restricted deficiency of GARP, which is a TGFβ-docking receptor that is important for the activation of TGFβ. ACT was more effective in controlling tumours in the mice with GARP-deficient platelets than in wild-type controls. However, ACT was not more effective in mice with TGFβ-deficient platelets, suggesting that the capacity of platelets to activate TGFβ — rather than their ability to function as a source of TGFβ — is responsible for their negative effect on ACT.

Finally, the authors showed that combining ACT with anti-platelet agents (aspirin and clopidogrel) enhanced the antitumour efficacy of ACT in mice with melanoma. They propose that targeting platelets could be a useful strategy to promote the efficacy of immunotherapies in human cancers.

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ORIGINAL ARTICLE Rachidi, S. *et al.* Platelets subvert T cell immunity against cancer via GARP–TGFβ axis. *Sci. Immunol.* **2**, eaai7911 (2017)