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## **GPVI inhibitor as anti-tumor gateway drug**

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In this issue of *Blood*, Volz et al. establish a potential anti-tumor strategy by exploiting the selective requirement for platelets to maintain vascular integrity within the tumor microenvironment.<sup>1</sup> Their work demonstrates, for the first time, that functional inhibition of platelet-specific surface receptor glycoprotein (GP) VI, using F(ab')<sub>2</sub> fragments to avoid platelet clearance, increases intratumoral hemorrhage and concomitant tumor cell apoptosis, as well as enhanced accumulation of chemotherapeutic drugs. These effects work additively to inhibit tumor growth, achieving results similar to those achieved by platelet depletion.<sup>2,3</sup>

Among platelet receptors, GPVI possesses the rare property of being nonessential for hemostasis but its loss or blockade prevents arterial thrombosis, making GPVI an attractive target. Indeed, Revacept, a soluble dimeric GPVI fusion protein, is currently in phase II trials as an anti-thrombotic therapy.<sup>4</sup> Platelets are small circulating anucleate cell fragments that are essential for hemostasis, but platelets are increasingly recognized as mediators of a broad range of hematologic functions. Platelets have been shown to safeguard the integrity of developing and dysfunctional vessels under inflammatory conditions. GPVI was recently established as an essential mediator of vascular integrity in inflammatory settings.<sup>5</sup> The tumor microenvironment is one such setting. The study by Volz et al. is the first to investigate this function of GPVI in solid tumors. Using both orthotopic and heterotopic models of tumor implantation in mice, they demonstrate increased intratumoral hemorrhage with either GPVI depletion in the host, or acute GPVI inhibition using an F(ab')<sub>2</sub> fragment of JAQ1 - an antibody that blocks the major collagen binding site on murine GPVI. The results achieved are similar to those obtained with acute platelet depletion.<sup>2,6</sup> The treatments directed against GPVI also increased the accumulation of chemotherapeutic drugs in the tumors. With anti-cancer drugs given every 4 days, the authors observed additive effects of GPVI inhibition or platelet depletion on tumor growth suppression. This provides proof of concept for combined GPVI targeting with chemotherapeutic drugs as a potentially effective anti-tumor approach targeting specific platelet functions but with minimal bleeding complications.

Unlike most current anti-platelet antibodies, the JAQ1 F(ab')<sub>2</sub> fragment does not lead to platelet clearance. Thus, the ability of JAQ1 F(ab')<sub>2</sub> to induce intratumoral hemorrhage can be attributed to molecular blockade of GPVI on circulating platelets, although contributions of plasma GPVI shed from platelets cannot be ruled out. This in itself is a striking result, as it indicates that GPVI exposure is the principal mediator of platelet-dependent vascular integrity. Of particular note is that mechanisms of GPVI-dependent vascular integrity in inflammation appear to vary depending upon the extent of vascular damage and the underlying context.<sup>7</sup> In the case of small breaks in the endothelial barrier exposing sub-endothelial collagen and laminin, single platelets can plug the leak via GPVI engagement in many inflammatory settings. This may be the case in dysfunctional tumor vasculature.<sup>8</sup> Indeed, Volz et al. were able to reproduce the hemorrhage and tumor growth inhibition of JAQ1 F(ab')<sub>2</sub> using soluble dimeric GPVI-Fc fusion protein, which competes for platelet-collagen binding, providing further support for this mechanism in the solid tumor models. However, GPVI inhibition caused massive intratumoral hemorrhage beyond what might be anticipated by single platelet-sized gaps in endothelium. Earlier studies demonstrated that infiltrating leukocytes are the major drivers of platelet-dependent intratumoral hemorrhage.<sup>9</sup> One possible explanation for the increased intratumoral hemorrhage in GPVI-blocked mice could involve multiple steps. GPVI is required initially to establish single platelet plugs via anchorage and spreading on sub-endothelial matrix. In the absence or blockade of GPVI, inflammatory cells – principally neutrophils – infiltrate and induce further vascular damage thereby increasing the extent of hemorrhage, as observed by Volz et al.<sup>1</sup> Neutrophil recruitment to the tumor microenvironment was not altered by GPVI inhibition, supporting a role for GPVI in either preventing or possibly repairing vascular damage induced from neutrophils. However, neutrophil depletion did not fully prevent hemorrhage by GPVI blockade, indicating contributions from other factors. Tumor-associated macrophages, other inflammatory cells, as well as plasma GPVI, may also play important roles. Moreover, platelet-derived permeability factors such as serotonin, vascular endothelial growth factor and

angiopoietin-1 have not yet been investigated in this context.<sup>2</sup> Dynamic studies of platelet and leukocyte interactions with the vessel wall in tumor models, coupled with analysis of soluble factors, will be essential to elucidating the cellular and molecular basis for intratumoral hemorrhage induced by GPVI blockade.

Platelets influence solid cancer progression through many mechanisms, and new roles for platelets are continually emerging. A striking outcome of the study from Volz et al. is the provocative notion that GPVI inhibition could have anti-cancer clinical utility by taking advantage of several of these mechanisms. First, GPVI inhibition caused tumor cell apoptosis and reduced growth of solid tumors by selectively driving intratumoral hemorrhage. Second, increased vascular permeability selectively in tumors potentiated intratumoral accumulation of commonly used cancer chemotherapeutics – both paclitaxel and liposomal doxorubicin. Third, GPVI depletion has been shown to limit metastatic dissemination in some ectopic tumor models in mice, although metastasis was not tested in this study.<sup>10</sup> While it is established that GPVI modulation blocks thrombosis but is permissive for hemostasis, GPVI blockade also appears to have no effect on integrity of intact vessels. Together, these properties of GPVI inhibition support an attractive multi-faceted approach to multi-stage cancer treatment, with potentially limited side effects compared to current anti-platelet therapeutic approaches. However, inflammation may present a substantial obstacle, as GPVI inhibition may also drive hemorrhagic responses at inflammatory sites other than the targeted tumor tissue. Hence, though GPVI blockade in combination with chemotherapeutic regimens may help deliver the triple-play to knock out malignancy, underlying inflammation may also be targeted with potentially dangerous results. It will be critical to determine whether effects of GPVI targeting in solid tumors reflect a common mechanism of increased hemorrhage at inflammatory sites, or if those effects are unique to the tumor microenvironment.

## **Footnotes**

Conflict of interest disclosure: The author declares no competing financial interests.

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