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Blood 142 (2023) 282–283

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

301.VASCULATURE, ENDOTHELIUM, THROMBOSIS AND PLATELETS: BASIC AND TRANSLATIONAL

Platelet Angiopoietin-1 Protects Against Experimental Lung Metastasis By Limiting Tumor Cell Extravasation

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In addition to their fundamental roles in hemostasis, platelets can contribute to both tumor growth and metastasis. However, despite being a reservoir for pro-angiogenic and metastatic cytokines, platelets also harbor negative regulators of tumor progression. One such regulator is angiopoietin-1 (Angpt1), an angiogenic cytokine that preserves vascular integrity by promoting cell-cell endothelial interactions downstream of its receptor, the receptor tyrosine kinase Tie-2. In addition, Angpt1 also protects against tumor cell metastasis through an unidentified mechanism. Although platelets are believed to be the primary source of Angpt1 in circulation, the contributions of platelet-derived Angpt1 to tumor growth and metastasis have not been investigated.

In this study, we demonstrate that platelet Angpt1 is selectively upregulated in the spontaneous PyMT breast cancer mouse model, but not pre-clinical models of melanoma or non-malignant inflammation (colitis), suggesting a distinct contribution of platelet Angpt1 in breast cancer. To test whether deletion of platelet Angpt1 affects tumor growth or metastasis, we generated mice selectively lacking Angpt1 in megakaryocytes and their platelet progeny (Angpt1 $^{fl/flPF4\ Cre}$, referred to as Angpt1 $^{Plt\ KO}$). Plasma Angpt1 was undetectable in Angpt1 $^{Plt\ KO}$ mice, comparable to mice deficient in the megakaryocyte differentiation factor thrombopoietin, which display approximately 10% of platelet counts. Taken together, these findings establish that platelets are the principal source of circulating Angpt1. In tumor implantation studies, orthotopic tumor growth and vascularization were unaffected in Angpt1 $^{Plt\ KO}$ mice in pre-clinical models of breast cancer and melanoma. However, Angpt1 $^{Plt\ KO}$ mice had increased experimental metastasis during both early (3-24 hours) and late (10 days, Figure 1) stages of tumor colonization in both breast cancer and melanoma models, revealing an important role for platelet Angpt1 in restraining the latter stages of tumor metastasis following tumor engraftment.

Next, we sought to mechanistically determine how platelet Angpt1 limits tumor cell metastasis. Static adhesion assays demonstrated that platelets lacking Angpt1 did not affect tumor cell attachment to endothelial cells when compared to platelets containing Angpt1. However, Angpt1 $^{Plt\ KO}$ mice had increased tumor cell retention and extravasation in their lungs following experimental metastasis (3-24 hours), suggesting that platelet Angpt1 limits endothelial permeabilization and the transendothelial migration of tumor cells out of blood vessels. Most importantly, all intravascular tumor cells were found within platelet-rich microthrombi immediately after sequestration in the lungs. We therefore conclude that localized Angpt1 released by activated platelets at the site of tumor cell arrest likely reprograms the surrounding endothelium to limit successful tumor cell extravasation. These findings reveal an unexpected role for platelets in restricting tumor cell metastasis.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-174399

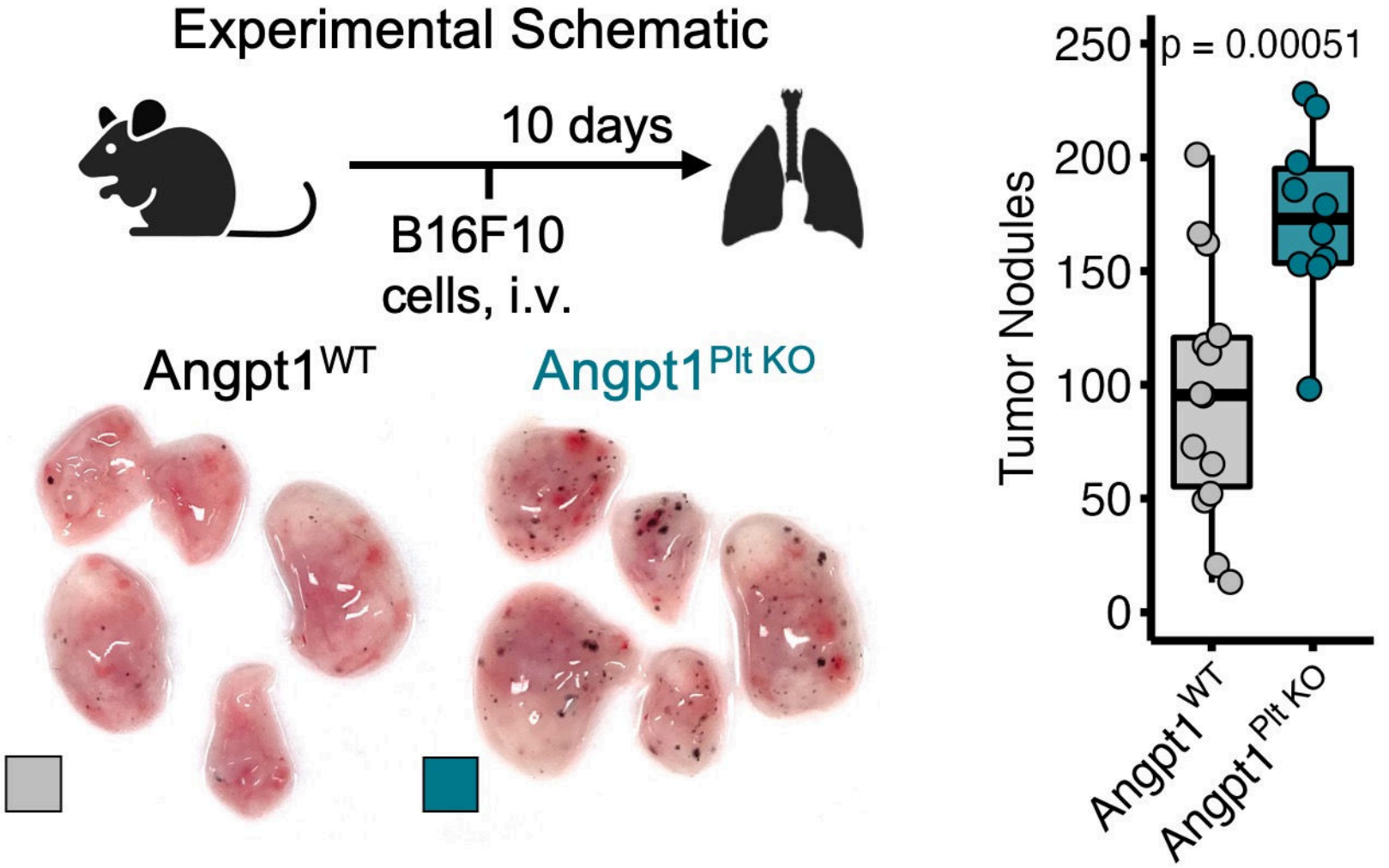

Figure 1. Platelet angiopoetin-1 protects against experimental metastasis. Wild-type mice (Angpt1^{WT}) and mice lacking platelet angiopoietin-1 (Angpt1$^{Plt\ KO}$) were intravenously injected with melanoma B16F10 cells and the number of lung tumor nodules **(A)** imaged and **(B)** quantified after 10 days. P-value determined from an unpaired two-tailed t.test.