Clotting and cancer progression: platelets count

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In knockout mice models of metastasis, platelets, activation of platelet protease-activated receptor 4 (PAR4), and fibrinogen/fibrin formation play key roles in the blood-borne metastasis of tumor cells with procoagulant activity, whereas activation of endothelial cell PAR1 and PAR2 does not appear to have a critical function in this process.

Activation of blood coagulation and platelets frequently occurs in cancer patients, and these patients acquire a hypercoagulable state. Multiple mechanisms account for this hypercoagulable state, but an important factor is that tumor cells express procoagulant molecules such as tissue factor (TF). Tumor cells also liberate cytokines that up-regulate TF on vascular endothelial cells and monocytes and cause platelet activation either directly or indirectly by the generation of thrombin. An ever-increasing number of studies suggest that rather than being just an epiphenomenon of malignancy, activation of blood coagulation and platelets serves to promote tumor progression.

Over 35 years ago, Gasic and colleagues implicated platelets in metastasis. Several blood coagulation proteins have also been found to be important in this process, including TF, factor VIIa, factor Xa, thrombin, and fibrinogen. The cellular effects of blood coagulation proteases are mediated by a unique family of receptors known as protease-activated receptors (PARs), of which there are 4 members (PAR1-4). These receptors are expressed on a variety of cells, including tumor cells, platelets, and vascular endothelial. However, what is not fully known is how platelets and the blood coagulation proteins promote tumor progression.

In this issue, Camerer and colleagues (page 397) report on the relative importance of platelets, platelet activation, fibrinogen, and endothelial cell PAR activation in blood-borne tumor metastasis. The authors combined gene knockout technology with a murine model of metastasis. Procoagulant-rich, B16-F10 murine melanoma cells were injected into the tail vein of mice and metastases in the lung determined after 2 weeks. Injection of the tumor cells into Nf-E2−/− mice, which lack circulating platelets, PAR4−/− mice, which have platelets that fail to respond to thrombin, and Fib−/− mice, which lack fibrinogen, resulted in markedly reduced lung metastases compared with wild-type mice. Treatment of the PAR4−/− mice with the specific thrombin inhibitor hirudin reduced the metastatic tumor burden further. Surprisingly, injection of the tumor cells into heterozygote PAR4+/− mice, which lack a bleeding phenotype, also demonstrated protection against metastasis, whereas injection of the cells into either PAR1−/− or PAR2−/− mice, which have impaired endothelial cell activation from blood coagulation proteases, did not prevent the formation of lung metastases. Results from this elegant study suggest that platelets, platelet activation involving PAR4, and fibrinogen/fibrin formation play key roles in blood-borne metastasis. In contrast, vascular endothelial cell activation by blood coagulation proteases does not appear to have a critical function in these murine models of metastasis.

Procoagulant activity of tumor cells promotes blood-borne metastases by multiple mechanisms. While the relative importance of tumor cell activation by thrombin, TF–factor VIIa complex, and factor Xa was not addressed by the authors, their findings highlight the major role of thrombin generation to activate platelets and form fibrin in tumor progression. Moreover, results from this study renew interest in taking aim at the platelet in general, and platelet PAR signaling pathways in particular, to prevent and control tumor metastases.

### REFERENCES