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Platelets Alter Tumor Cell Attributes to Propel Metastasis: Programming in Transit

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Metastasis of epithelial tumors critically depends on acquisition of a disseminating phenotype that allows tumor cells to colonize distant organs. In this issue of *Cancer Cell*, Labelle et al. demonstrate that an epithelial-mesenchymal-like transition can be induced by interaction between platelets and tumor cells.

Host cell types provide cues that regulate tumor metastasis, essentially at all stages of tumor progression. Cells disseminating from primary epithelial tumors use the bloodstream and lymphatics to colonize distant sites. The impact of tumor-host interactions encountered within the bloodstream has been explored far less than that occurring in primary tumors and distant lesions. There are primarily three reasons: microenvironments within the vasculature are difficult to access, hard to define, and transient in nature. While cancer patients often present with conditions indicating activation of platelets and the coagulation system, the role of platelets in cancer dissemination is only partially understood (Erpenbeck and Schön, 2010; Gay and Felding-Habermann, 2011). In this issue of *Cancer Cell*, Labelle et al. (2011) demonstrate a novel role for platelets that profoundly impacts the ability of blood borne tumor cells to seed distant metastases. Direct platelet signaling to tumor cells leads to enhanced metastasis through platelet release of transforming growth factor β (TGF-β) which induces epithelial-mesenchymal-like transition in tumor cells and is critically enhanced through direct tumor cell-platelet contact.

Platelets are key contributors to hemostasis, leukocyte trafficking during inflammation, and maintenance of vessel stability. A hallmark of platelet function is the prevention of hemorrhage and perpetuation of coagulation to form and stabilize blood clots. Platelets are implicated in supporting metastasis through coherence with tumor cells, formation of heteroaggregates that also include leukocytes (Läubli et al., 2006), and proteins of the coagulation system that provide a transient microenvironment, which supports tumor cell survival and protection from immune elimination (Palumbo et al., 2005).

As the links between platelets, coagulation, and tumor metastasis coalesce, platelet-specific factors and recipient signaling mechanisms on tumor cells, important for malignancy, are still being resolved in mouse models. Labelle et al. (2011) now identify specific platelet factor and signaling pathways evoked in tumor cells that critically support metastasis. By conditioning tumor cells with platelets in vitro, the authors elicit colon and breast carcinoma cells to become more invasive and mesenchymal-like and ultimately more aggressive in an experimental lung metastasis model. This enhanced metastasis shows that the initial exposure to platelets can reprogram tumor cells. Thus, these results extend beyond documented contributions of platelets to tumor cell arrest, survival, and immune evasion en route to metastasis (Figure 1). Signaling factors released from platelet granules could directly affect tumor cell survival, proliferation, or invasiveness during metastasis. In a definitive and beautifully-executed experiment, Labelle et al. (2011) knockout expression of TGF-β1 specifically in megakaryocytes, and hence in platelets, by generating a TGF-β1 floxed/platelet factor 4 cre mouse model (*Pf4-cre*$^{+}$*; TGFβ1*$^{fl/fl}$). The dramatically diminished metastasis seen in mice deficient in platelet TGF-β1 suggests that tumor cell behavior is altered as a result of platelet activation and release of alpha granules. A lack of TGF-β1 in platelets also delayed tumor cell extravasation in

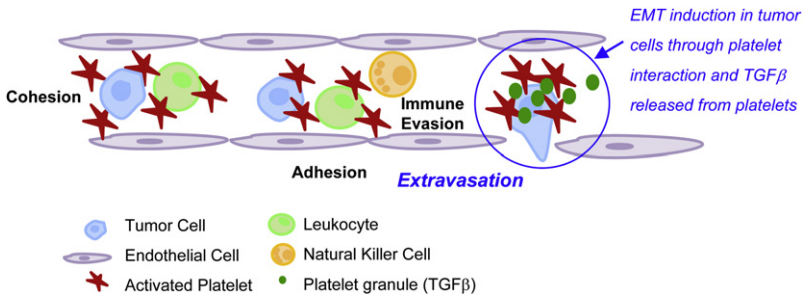

Figure 1. Steps in Hematogenous Metastasis that Are Critically Supported by Platelets
Platelets contribute to generating a microenvironment for tumor cells within the bloodstream that supports the metastatic process. Upon activation, platelets undergo a shape change and release granules that contain growth factors, chemokines, and proteases. Activated platelets also increase their adhesiveness, which fosters cohesion with tumor cells and leukocytes to form heteroaggregates which interact with the endothelium as well as protect tumor cells from immune elimination. In this issue of *Cancer Cell*, Labelle et al. (2011) identify a new role for platelets and a mechanism through which platelets interact with tumor cells to become more invasive and capable of colonizing the lung. Platelets release TGF-β that induces tumor cells to express genes for epithelial-mesenchymal-like transition while in contact with platelets.

the lung, indicating that platelets can expedite tumor cell exit from the vasculature and thus enhance lung metastasis. This approach takes into account the in vivo exposure of tumor cells within the bloodstream to endogenous TGF-β1. The use of megakaryocyte lineage-specific gene deletion distinguishes the platelet source from that of many other vascular cell types and from additional platelet contributions to metastasis. Corroborating this result, the authors show that priming of cancer cells by platelets is in part reversed by TGF-β1 depletion in platelets. These data indicate that platelet factors can act directly on tumor cells to enhance metastasis.

TGF-β1 was previously shown to prime metastasis to the lungs (Padua et al., 2008). Labelle et al. (2011) therefore define platelets as a source for TGF-β1 in addition to the well established tumor stromal and induced autocrine TGF-β1 production in tumor cells (Yang et al., 2010). Platelet-derived TGF-β1 has been reported to suppress lysis of tumor cells by natural killer cells in vitro (Kopp et al., 2009). Factors released by platelets may therefore alter the behavior of both cancer and immune cells to enhance the aggressiveness and survival of circulating tumor cells. In agreement with this concept, another platelet-released factor, lysophosphatidic acid, has been shown to impact metastasis. Platelet lysophosphatidic acid can induce tumor cell signaling to promote bone metastasis (Boucharaba et al., 2004). Although TGF-β1 appears to be a major determinant of lung metastasis, additional undefined platelet factors may signal to tumor or host cells, and thereby contribute to metastasis in multiple organs.

Tumor cells entering the bloodstream within a primary tumor coordinate with stromal cells to invade surrounding tissue, remodel its matrix, and access the circulation. Activation of epithelial-mesenchymal transition (EMT) results in decreased intercellular adhesion and cell polarity as well as an increase in matrix remodeling and migration to promote metastasis (Kalluri and Weinberg, 2009). Labelle et al. (2011) contribute new insight by uncovering that EMT can be activated by TGF-β secreted from surrounding platelets. The authors report that platelets trigger activation of TGF-β/Smad signaling to endow tumor cells with a more aggressive phenotype. The interaction with platelets likely synergizes with cues received in the primary tumor to generate, reinforce, and amplify an EMT program that ultimately supports colonization of distant sites.

Several platelet receptors have been reported to support metastasis. Labelle et al. (2011) show that tumor cell contact with a platelet pellet, but not platelet releasate alone, primes an increase in metastasis through induction of epithelial to mesenchymal-like genes. This induction involves NF-κB pathway activation, because inhibition of this pathway via tumor cell-expressed IκBα superrepressor reversed the priming effect of platelets on invasion, mesenchymal-like gene expression, and metastasis (Labelle et al., 2011). Programming of cancer cell aggressiveness thus involves coordination of cancer cell contact with platelets, and signaling in response to platelet releasate. The intersection between TGF-β/Smad signaling with contact-driven NF-κB pathways may cooperate in promoting tumor malignancy. Future studies using defined cancer cell systems and transgenic mouse models will help identify the functional interactions between tumor cells and platelets that drive this pathway activity.

Together, Labelle et al. (2011) contribute new insight into direct tumor cell-platelet interactions that induce mesenchymal-like attributes in metastatic cells. The study suggests that tumor cells, which have left the primary tumor, continue to interact with and respond to cues from changing host microenvironments to establish distant lesions. Discovery of platelet interaction and their released TGF-β as enhancer of metastatic activity defines potential new therapeutic targets for prevention and treatment of metastatic disease, possibly without disturbing platelet functions in hemostasis.

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