Editorial

Tamoxifen Suppresses Platelet Activation-Supported Angiogenesis and Metastasis

Pavel Davizon-Castillo, Jorge Di Paola

It has been known for decades that platelets are critical for providing adequate hemostasis. However, more recently, platelets have been implicated in other health- and disease-related processes, such as angiogenesis, wound healing, inflammation, tumor progression, and metastasis.[1–4] Platelet interactions with tumor cells occur locally at the tissue level and also in the blood circulation. These interactions can lead to platelet activation, a process that results in the release of the contents of platelet granules to the tumor microenvironment. This platelet releasate includes large amounts of bioactive molecules which facilitate tumor growth, endothelial transmigration, and angiogenesis.[5] In the bloodstream, platelets are also able to form aggregates with circulating tumor cells. As the platelets adhere to the circulating tumor cells' surfaces, this interaction can generate a shielding effect by facilitating immune evasion and preventing clearance of cancer cells. In addition, the interaction of platelets with circulating tumor cells can also promote epithelial to mesenchymal transition, a process that favors tumor growth and increases metastatic burden.[1] Therefore, it has become evident that by several distinctive mechanisms, platelets promote tumor progression and metastasis.

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Tamoxifen is a chemotherapeutic agent that has been widely used over the past 40 years as endocrine therapy for estrogen-receptor positive (ER^+) breast cancer. Tamoxifen is known to block estrogen receptors, therefore, disrupting important signaling pathways in tumor cells (process known as estrogen deprivation). In the current issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Johnson et al[6] characterize an indirect platelet-mediated pathway by which Tamoxifen and its metabolite, 4-hydroxytamoxifen (4-OH), inhibit angiogenesis and metastasis (Figure). The investigators show that platelets from patients taking tamoxifen are less responsive to activation by the breast tumor cell line MCF-7. Moreover, the releasate from these platelets contain less vascular endothelial growth factor which, in vitro, results in decreased capillary tube formation, a surrogate marker of angiogenesis.

The main conclusions of this study are supported by an extensive and convincing series of experiments that demonstrate the effect of Tamoxifen and its metabolite on platelet activation. The investigators show that platelets incubated with Tamoxifen or 4-OH exhibit decreased activation responses on stimulation with ADP or exposure to the cell line MCF-7. Interestingly, exposure to 4-OH also blocks the activation of platelets by the strong agonist thrombin-related activation peptide and the triple-negative tumor cell line MDA-MB-231. To confirm that this effect has functional consequences, the releasate of platelets exposed in vitro to Tamoxifen or 4-OH did not support the formation of capillary tubes when compared with controls. Furthermore, protein analysis by ELISA and membrane-based protein arrays of the releasates of platelets exposed to Tamoxifen or 4-OH show that the observed differences are associated with the release of significantly lower amounts of key proangiogenic molecules, such as vascular endothelial growth factor, and higher amounts of potent antiangiogenic mediators, such as angiopoietin-1. Finally, in vitro invasion assays demonstrated that cancer cells exposed to the releasate of platelets treated with Tamoxifen or 4-OH had decreased migration, indicating that these cancer cells have less metastatic potential.

Although this work is of clear significance and paves the road for further investigations, there are still many unanswered questions. The specific mechanism(s) by which Tamoxifen and 4-OH modulate platelet activity is not completely understood. Although platelets have estrogen receptors, it has previously been shown that inhibition of those receptors does not abrogate platelet responses to Tamoxifen. The mechanism of action of Tamoxifen or 4-OH could alternatively be explained by an effect on thrombopoiesis, perhaps facilitating selective packaging of platelet α-granules with antiangiogenic content generating platelet populations with less proangiogenic/metastatic potential.

Interestingly, by modulating platelet activation, Tamoxifen could potentially also contribute to decreasing the incidence of cancer-associated thrombosis in patients with breast cancer.

Johnson et al[6] findings should, however, offer a cautionary note to scientists using genetic animal models that rely on the administration of Tamoxifen to express or silence genes in models of metastasis or thrombosis and hemostasis given the proposed effect of Tamoxifen on platelet function, angiogenesis, and metastasis.

In summary, Johnson et al[6] have characterized a platelet-mediated pathway by which Tamoxifen and its metabolite 4-OH indirectly restrain angiogenesis and metastasis. Although these compounds directly affect breast cancer cells by causing estrogen deprivation, platelets exposed to Tamoxifen can potentially limit tumor progression in situ

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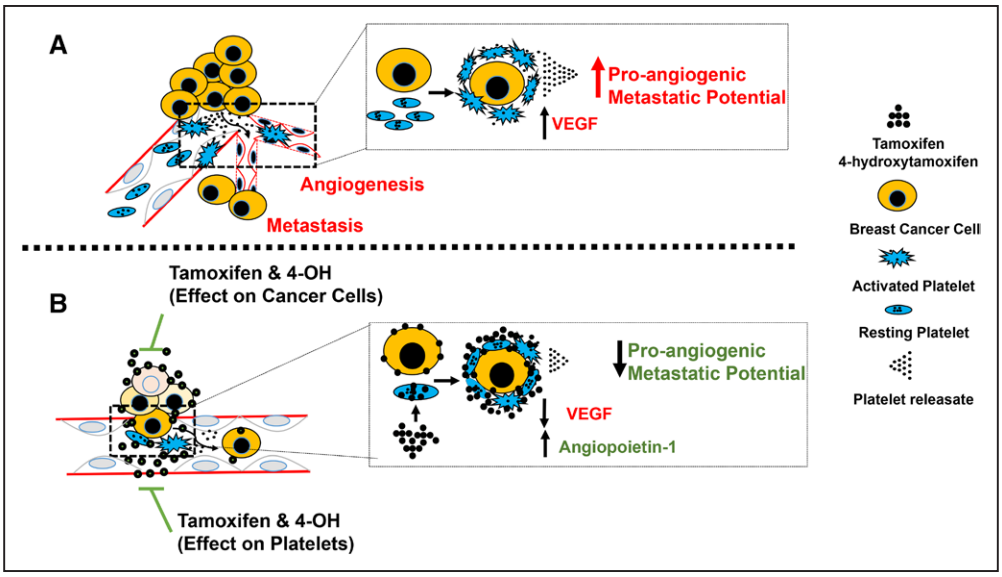

Figure 1. A, Cancer cells can interact with platelets and trigger platelet activation. The platelet releasate contains high amounts of the proangiogenic molecule vascular endothelial growth factor (VEGF), promoting angiogenesis and metastasis. **B**, Tamoxifen and its metabolite 4-hydroxytamoxifen (4-OH) act directly on tumor cells and platelets. On platelets, Tamoxifen decreases the activation effect of cancer cells. The platelet releasate of these platelets contains lower amounts of the proangiogenic molecule VEGF and higher levels of the antiangiogenic molecule angiopoietin-1.

(providing less proangiogenic signals) and hinder the metastatic burden of circulating tumor cells.

Disclosures

None.

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