



# A dynamic platelet—tumor cell axis

Adam Corken, Jerry Ware

Department of Physiology & Biophysics, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Correspondence to: Jerry Ware. Department of Physiology & Biophysics, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA.  
Email: jware@uams.edu.

Comment on: Xu XR, Yousef GM, Ni H. Cancer and platelet crosstalk: opportunities and challenges for aspirin and other antiplatelet agents. *Blood* 2018;131:1777-89.

Received: 29 August 2018; Accepted: 03 December 2018; Published: 07 December 2018.

doi: 10.21037/aob.2018.12.01

View this article at: <http://dx.doi.org/10.21037/aob.2018.12.01>

A dynamic reciprocating crosstalk between cancer cells and platelets presents both opportunities and challenges for an increased understanding of tumorigenesis and improved patient therapies (1). The importance of understanding this relationship finds merit in the widespread use of cardiovascular therapies that target normal platelet function but impact diseases seemingly unrelated to hemostasis or thrombosis (2). In the case of cancer, there exists expanding databases to support anti-cancer effects for common medications, such as aspirin (3). However, major questions remain for “how, where, and when” aspirin exerts its effect on the progression of cancer. A systematic approach for understanding the “how, when and where” question can be based on defining the platelet’s relevance within each component of the “hallmarks of cancer” (4-6).

Xu *et al.* elegantly define how cancer changes the circulating platelet via bidirectional pathways (1). Documented first are the tumor-induced effects on the platelet, such as; increased platelet aggregation, induced platelet vesicle release, changes in the platelet RNA profile, and enhanced thrombopoiesis. Cumulatively, the tumor cell hijacks the normal hemostatic function of the platelet generating a pro-thrombotic platelet. This becomes beneficial for the tumor cell as will be described below. However, immediately it becomes apparent “how” anti-platelet therapies could impact the tumor cell or more importantly the progression of cancer.

Tumor cell induced phenotypic changes to the platelet allow for the cancer cell to commandeer the platelet’s intracellular cargo (*ex.* soluble mediators and RNA content), boost mitogenic signaling, and promote tumor vascularization (7,8). Likewise, cancer cells elicit platelet

aggregation which can serve to shield the tumor from immune surveillance and deletion (9). Thus, therapeutic manipulation of the platelet-cancer interface, with widely utilized anti-platelet agents, is now recognized with potential anti-cancer benefits. Xu and colleagues have summarized the consequences of platelet-dependent effects mediated by tumor cells and the possible mechanistic benefits of aspirin (1).

Having established the changes in platelet phenotype induced by tumor cells, the bidirectional effect of platelets on the tumor cell must be considered. Globally, it is recognized that platelets support tumor growth and metastasis. The “how” can be appreciated with an even older cancer adage—“tumors, wounds that do not heal” (10). Beyond the well-recognized hemostatic function, platelets are well equipped to promote wound healing. Loaded with a myriad of growth factors and proangiogenic proteins, the activated platelet is a wound healing machine (11). Thus, platelets contribute to tumor growth by providing a sustainable signal to the tumor cell for proliferation, an ability to resist cell death, and promote vascularization for the insatiable appetite of the growing tumor (1).

Providing the primary tumor with the equivalent of “fertilizer” for growth, the platelet further contributes to metastasis at distant sites (12,13). Here, the importance of metastasis in the cancer prognosis cannot be understated (14). Indeed, the diagnosis of metastatic disease is most commonly met with a more unfavorable outcome. Platelets have the ability to elicit an epithelial-mesenchymal transition (EMT) for tumor cells that provides the cell with an ability to effectively migrate and intravasate into the bloodstream (12). Once in the bloodstream, the tumor

cell is exposed to a very harsh environment and an immune system designed to destroy the tumor cell. However, the altered phenotype of the platelet effectively “cloaks” the circulating cancer cell providing the cancer cell a shield to evade immune destruction effectively promoting cell survival in the blood circulation (9,15). Finally, at a distant metastatic site the tumor cell-associated platelet confers adhesive function to the aggregate for arrest at the endothelium, extravasation, and seeding of the tumor at the distant site (1). Thus, elaborate cross-talk between platelet and tumors participate in multiple steps defined by the “hallmarks of cancer” and explain the “how” for a platelet’s contribution to tumorigenesis (5).

When considering the “where” for platelet involvement, typically the focus is at a site of vascular damage. Indeed, the platelets’ ability to recognize vascular damage and aggregate has been extensively characterized (16). In the case of cancer, the platelet-cancer cell crosstalk is facilitated by a burgeoning tumor microenvironment which recruits platelets to aid in tumor development. The microenvironment “reprograms” platelet “behavior” to produce “tumor-educated platelets” or TEPs (17). The mechanisms by which platelet function is redirected by cancer are not well known but what is known is the means by which platelets can exacerbate the tumor burden. Since platelets have an extensive secretome, TEPs are coerced into releasing factors that promote tumor growth, EMT, angiogenesis and metastasis (as described above). In addition, platelet miRNAs delivered via exosomes and microparticles can alter tumor gene expression and subsequently heighten malignancy. Additionally, tumor cell-induced platelet aggregation (TCIPA) generates platelet-platelet and platelet-tumor cells interactions using a number of platelet adhesion receptors (18). The result is a platelet barrier which aids the tumor in evading immune detection and enhances metastasis, a process that occurs both at the site of the primary tumor, within the bloodstream, and finally at a distant metastatic site.

Defining the “when” in the platelet-tumor cell axis brings up the opportunity for pharmacologic intervention (19). With the “how” and “where” identified, the issue of when a given therapy might pose an opportunity or a challenge becomes the final thought (1). For decades’ aspirin has been utilized as an inhibitor of platelet activity to curtail incidences of cardiovascular disease (CVD). COX-1 in platelets is vital to the production of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) which is a potent platelet agonist which aids in platelet activation and aggregation. Thus, aspirin is

widely prescribed as a frontline therapeutic for those individuals who present with a heightened risk for CVD. The prevalence of aspirin consumption has serendipitously yielded a host of clinical data to implicate the anti-platelet role of aspirin as an avenue for mitigating cancer development (3,20,21).

Recently, the anti-platelet and anti-inflammatory agent aspirin has been rising above the milieu of widely prescribed pharmaceuticals as a potential cancer prophylactic. As a cyclooxygenase (COX) inhibitor, aspirin has been speculated to provide anti-tumor effects for those cancers which overexpress COX-2. This particular COX isoform is not widely expressed under normal conditions but has been found to be in cells from several types of cancers. COX-2, along with COX-1, converts arachidonic acid into a precursor of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). The increase in PGE<sub>2</sub> synthesis enhances tumor progression as the pleiotropic effect of PGE<sub>2</sub> augments several hallmarks of cancer. It is through the inhibition of this pathway that many believe the anti-cancer effectiveness of aspirin is derived. However current understandings of platelet contributions to cancer pathology have led some to hypothesize that aspirin’s anti-cancer effects are chiefly due to its anti-platelet function.

Clinical and pharmacological studies have demonstrated that doses of 75–300 mg/day of aspirin diminish the prevalence of cancer and subsequently cancer related deaths. Interestingly, the low dose (75 mg/day) and once daily regimens of aspirin prescription demonstrated the same level of effectiveness as higher doses. Due to the short half-life of aspirin, *de novo* synthesis of new COX proteins by nucleated cells would circumvent the aspirin activity in a relatively short timeframe. However, because platelets are anucleated, the restoration of functional COX activity within the platelet population will only occur with the release of newly synthesized platelets into the circulation. As the genesis of new platelets occurs over a broader period than protein synthesis, many now believe that the efficacy of low/delayed dosages of aspirin is due primarily to an inhibition of platelet function. However, going forward major questions still remain as to how much of the aspirin-dependent effect is platelet-centric, tumor cell-centric, or another cell.

Currently, the results suggest the anti-cancer mechanism of aspirin may primarily lie in mitigating the platelet contribution to tumorigenesis and less in direct targeting of cancer cells. Furthermore, similar findings have been found in several classes of cancers such as colorectal, breast and pancreatic. Another possible mechanism of aspirin-

mediated anti-platelet activity is that aspirin has been shown to activate ADAM17 (TACE) which acts to cleave glycoprotein Ib $\alpha$  (GPIb $\alpha$ ) from the platelet surface (22). Though not a proposed mode of platelet-targeted anti-tumor activity, the loss of GPIb $\alpha$  from the platelet's surface would have a significant impact on TCIPA facilitated by this receptor. Regardless of the specific route by which platelet function is impaired, it has become clear that aspirin is showing promise as a first-line preventative of tumor progression (1,23,24).

As platelet adhesion and activation utilizes a broad population of receptors there are several known, and developing, antagonists previously intended for CVD that could be applied as cancer treatments. Currently aspirin is the only drug with significant clinical data but depending on how platelets participate in a particular cancer, other pharmacological options could also be deemed viable. In particular, the class of therapies targeting the P2Y<sub>12</sub> platelet purinergic receptor which are often times taken with low dose aspirin has been strongly implicated (24). It is important to note that while many studies suggest platelets to be supportive in tumor progression, they are a dynamic participant that can inhibit tumor proliferation and migration. In the context of inflammation, platelets have been shown to be both pro- or anti-inflammatory depending on the specific context in which inflammation is triggered (25). Therefore, it stands to reason that platelets will have a dynamic impact in tumor biology. As such, it is important to be rigorous in the determination of whether targeting platelets is beneficial (1). This will have to be balanced with individual patient tolerance to aspirin medication.

To summarize, the dynamic conditions surrounding tumorigenesis results in substantial heterogeneity within cancers even if derived from the same tissue. Accordingly, our understanding of platelet biology is continuing to expand wherein platelets are now included as active participants in the processes of inflammation and tumor progression (6). However, the exact nature of platelet participation varies depending on circumstantial criteria whereupon platelets may act as either allies or adversaries of cancer outgrowth. In spite of these considerations, aspirin-mediated platelet inhibition has been shown to mitigate the tumor burden in several different cancers. It is also possible that COX-2 inhibition within cancer cells directly synergizes with the platelet-inhibiting function of aspirin but supplemental experiments seem to attribute anti-cancer effectiveness primarily to platelet-dependent effects. Thus,

aspirin and other anti-thrombotic therapies should receive careful consideration in the fight against cancer ranging from a possible frontline preventative to a supplemental agent in a therapeutic regiment.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned and reviewed by the Section Editor Dr. Xiuzhang Xu (Guangzhou Blood Center, Guangzhou, China).

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aob.2018.12.01>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. Xu XR, Yousef GM, Ni H. Cancer and platelet crosstalk: opportunities and challenges for aspirin and other antiplatelet agents. *Blood* 2018;131:1777-89.
2. Leslie M. Cell biology. Beyond clotting: the powers of platelets. *Science* 2010;328:562-4.
3. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* 2012;379:1602-12.
4. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*

- 2000;100:57-70.
5. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646-74.
  6. Franco AT, Corken A, Ware J. Platelets at the interface of thrombosis, inflammation, and cancer. *Blood* 2015;126:582-8.
  7. Pinedo HM, Verheul HM, D'Amato RJ, et al. Involvement of platelets in tumour angiogenesis? *Lancet* 1998;352:1775-7.
  8. Peterson JE, Zurakowski D, Italiano Jr JE, et al. VEGF, PF4 and PDGF are elevated in platelets of colorectal cancer patients. *Angiogenesis* 2012;15:265-73.
  9. Palumbo JS, Talmage KE, Massari JV, et al. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. *Blood* 2005;105:178-85.
  10. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med* 1986;315:1650-9.
  11. Menter DG, Kopetz S, Hawk E, et al. Platelet "first responders" in wound response, cancer, and metastasis. *Cancer Metastasis Rev* 2017;36:199-213.
  12. Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. *Cancer Cell* 2011;20:576-90.
  13. Labelle M, Hynes RO. The initial hours of metastasis: the importance of cooperative host-tumor cell interactions during hematogenous dissemination. *Cancer Discov* 2012;2:1091-9.
  14. Lambert AW, Pattabiraman DR, Weinberg RA. Emerging Biological Principles of Metastasis. *Cell* 2017;168:670-91.
  15. Nieswandt B, Hafner M, Echtenacher B, et al. Lysis of tumor cells by natural killer cells in mice is impeded by platelets. *Cancer Res* 1999;59:1295-300.
  16. Michelson AD. Platelets. 3rd edition. New York: Academic Press, 2013.
  17. Best MG, Sol N, Kooi I, et al. RNA-Seq of Tumor-Educated Platelets Enables Blood-Based Pan-Cancer, Multiclass, and Molecular Pathway Cancer Diagnostics. *Cancer Cell* 2015;28:666-76.
  18. Jurasz P, Alonso-Escolano D, Radomski MW. Platelet-cancer interactions: mechanisms and pharmacology of tumour cell-induced platelet aggregation. *Br J Pharmacol* 2004;143:819-26.
  19. Gresele P, Momi S, Malvestiti M, et al. Platelet-targeted pharmacologic treatments as anti-cancer therapy. *Cancer Metastasis Rev* 2017;36:331-55.
  20. Kaiser J. Will an aspirin a day keep cancer away? *Science* 2012;337:1471-3.
  21. Rothwell PM, Wilson M, Price JF, et al. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet* 2012;379:1591-601.
  22. Jansen AJ, Josefsson EC, Rumjantseva V, et al. Desialylation accelerates platelet clearance after refrigeration and initiates GPIIb metalloproteinase-mediated cleavage in mice. *Blood* 2012;119:1263-73.
  23. Ware J, Corken A, Khetpal R. Platelet function beyond hemostasis and thrombosis. *Current opinion in hematology* 2013;20:451-6.
  24. Leader A, Zelikson-Saporta R, Pereg D, et al. The Effect of Combined Aspirin and Clopidogrel Treatment on Cancer Incidence. *Am J Med* 2017;130:826-32.
  25. Corken A, Russell S, Dent J, et al. Platelet glycoprotein Ib-IX as a regulator of systemic inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2014;34:996-1001.

doi: 10.21037/aob.2018.12.01

**Cite this article as:** Corken A, Ware J. A dynamic platelet—tumor cell axis. *Ann Blood* 2018;3:47.