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Carpe low-dose aspirin: the new anti-cancer face of an old anti-platelet drug

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Abstract

Cancer metastasis is a dynamic process during which cancer cells separate from a primary tumor, migrate through the vessel wall into the bloodstream, and extravasate at distant sites to form secondary colonies. During this process, circulating tumor cells are subjected to shear stress forces from blood flow, and in contact with plasma proteins and blood cells of the immune and hemostatic system, including platelets. Many studies have shown an association between high platelet count and cancer metastasis, suggesting that platelets may play an occult role in tumorigenesis. This mini-review summarizes recent and emerging discoveries of mechanisms by which cancer cells activate platelets and the role of activated platelets in promoting tumor growth and metastasis. Moreover, the review discusses how aspirin has the potential for being clinically used as an adjuvant in cancer therapy.

Introduction.

Emerging evidence suggests that platelets, as dynamic and multifunctional blood cells, facilitate the malignant growth and metastatic spread of cancer cells. From studies exploiting *in vitro* platelet-cancer cell co-culture systems and *in vivo* thrombocytopenic mouse models

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of cancer, it is now evident that direct or indirect interactions of cancer cells with platelets lead to their reciprocal activation and release of soluble mediators, creating a microenvironment that promotes both platelet activation and cancer progression.[1; 2] Further evidence for the role of platelets in cancer progression has come from epidemiological studies that show a connection between the use of low-dose aspirin, an anti-platelet drug, and reduction in cancer metastasis and duration, specifically for colon tumors.[3–5] The main focus of this review is to provide an updated overview on the role of platelets in cancer progression. We particularly highlight mechanisms through which growth factors released by platelets send proliferative and metastatic signals to cancer cells. We briefly summarize studies that explore the relationship between platelet count and cancer progression. Finally, we discuss the potential for aspirin to regulate the cross-talk between platelets and cancer cells and share recommendations for the use of aspirin for anti-cancer therapy.

Platelets and cancer: new data on old friends.

The insight that platelets are endowed with the mitogenic power required for tumor progression and metastasis was recognized over 50 years ago.[6] Since then, tremendous progress has been made in the identification of relevant molecular mediators and signaling pathways that are required for the regulation of metastatic cancers by platelets. Accumulating evidence supports the notion that circulating tumor cell survival, extravasation, angiogenesis and growth at sites of metastasis are largely regulated by the platelet secretome, platelet-derived microparticles (MPs) and platelet membrane-bound molecules that are functionally linked to the activation of metastatic pathways in cancer cells.[1] One centrally important process by which platelets promote cancer metastasis is their activation in circulation, which can occur relatively early in the metastatic process.[7] Mechanisms of platelet-cancer interactions have been extensively studied in recent years and involve direct activation of platelets via physical engagement of platelet receptors, including $P2Y_{12}$, integrin $\alpha_{IIb}\beta_3$, P-selectin and CLEC-2, and indirect activation of platelets via tumor-derived platelet agonists, mainly thrombin and ADP.[1; 8–12] Recently, Cho et al. demonstrated that ovarian cancer-derived ADP activates platelet $P2Y_{12}$ receptors, which in turn induces platelets to release growth factors required for ovarian tumor growth.[9; 13] Moreover, platelet-specific depletion of apoptosis signal-regulating kinase 1 (Ask1) *in vivo* caused defects in ADP-$P2Y_{12}$-dependent activation and reduced metastasis of lung tumor cells, supporting targeting these pathways to attenuate ovarian and lung cancer metastasis.[14]

Growth factors released by activated platelets are among the major players through which platelets contribute to cancer progression. Importantly, the type of platelet-derived growth factor required to elicit molecular signaling in cancer cells is partly dependent on the cell type. Recent studies have highlighted a role for platelet-derived transforming growth factor β (TGFβ) in facilitating cancer metastasis. Rachidi and colleagues demonstrated via platelet-specific TGFβ KO mice that platelets are the most important systemic source of TGFβ affecting tumor growth and metastasis.[15] Importantly, it has been reported that TGFβ is released by platelets predominantly in response to podoplanin-expressing cancer cells.[16] Platelet-derived TGFβ has been shown to significantly contribute to the paracrine

mesenchymal transformation of epithelial cancer cells, including colon, breast and ovarian carcinoma, and to the direct suppression of the anti-tumor activity of immune cells such as natural killer (NK) and cytotoxic $CD4^+$ and $CD8^+$ T cells, enhancing tumor survival and invasion.[15; 17–19] Among other platelet-derived cytokines involved in cancer progression, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and epithelial growth factor (EGF) have also been proposed.[20–22] Moreover, platelets from cancer-bearing mice display significant alterations in their secretome profile, including presence of tumor-derived cytokines.[23–25] Similarly, increased levels of thrombopoietin, tumor necrosis factor α and granulocyte colony-stimulating factor have been detected in the secretome of platelets activated by cancer cells.[24] Nevertheless, the mechanisms driving the platelet secretome towards a more tumorigenic state are not known, and the contribution of this process to oncogenesis remains to be defined. Notably, there is some evidence that platelets can uptake growth regulators from the circulation, suggesting that platelets have the ability to sequester extracellular proteins.[25] The diversity and relative abundance of proteins sequestered by tumor-exposed platelets, and the relationship between platelet sequesterome and secretome are not known. Ultimately, the platelet sequesterome and secretome may represent useful biomarker sources to identify specific tumor fingerprints.

Another way through which platelets may facilitate tumor progression is the release of microparticles (MPs). MPs are membrane vesicles released by activated or apoptotic platelets that can signal to distal cancer cells and modify their phenotype.[26] How platelet MPs support cancer cell metastasis is a fundamental question that is just beginning to be answered. Platelets MPs have been shown to promote the synthesis and secretion of metalloproteinases (MMP-2, MMP-9 and MMP-1) and IL-8 from prostate cancer cells, which aids in the invasive step of cancer metastasis.[27] Similarly, platelet MPs induce an invasive phenotype in malignant hematopoietic cells and breast cancer cells, which is mediated by a synergistic activation of MAPK and PI3K-AKT intracellular signaling.[28; 29] Besides growth factors and microparticles, platelet surface receptors have been implicated in cancer metastasis. Pharmacological blockade of platelet integrin $\alpha_{IIb}\beta_3$ and/or P-selectin significanty reduces the aggressive behaviour of tumor cells *in vitro*, and knockdown of P-selectin leads to strong reduction in tumor growth *in vivo*.[30–32]

Tumor cells and their products are not only capable of activating platelets but also promoting thrombopoiesis, and, perhaps relatedly, thrombocytosis is a common pathological outcome of cancer.[33–35] As discussed further in the section below, cancer-induced thrombocytosis has largely been attributed to excessive release of cancer cell IL-6, a cytokine that triggers the hepatic synthesis of thrombopoietin to drive thrombopoiesis.[33] Recently, Pucci et al. identified platelet factor 4 (PF4) as an endocrine signal released by lung cancer cells that induces platelet production and accumulation in murine lungs.[36] Further studies are required to understand whether inhibition of pathways causing cancer-induced thrombocytosis or targeted regulation of platelet count are viable therapeutic approaches to limit platelet-cancer cell communication.

Platelet count and cancer progression.

The association of thrombocytosis with cancer is related to the type and stage of cancer. For example, the occurrence of thrombocytosis in patients with breast cancer was reported to only be 3–5%, while in patients with colorectal cancer, it was 46–64%.[37; 38] Thrombocytosis is also more prevalent in patients with late stage cancers.[38–41]

Perioperative platelet counts exceeding 400,000/μL are an independent predictor of worse outcomes for patients with cancer.[37–42] However, the majority of studies were conducted with single platelet count measurements around the time of diagnosis or treatment, which might be susceptible to endogenous and exogenous factors, even if measures have been taken to exclude known causes of reactive thrombocytosis. The cause of the thrombocytosis in these studies remains unknown. However, one study in patients with ovarian cancer proposed a role for cancer in platelet production through the promotion of megakaryocytopoiesis by tumor-derived humoral agents such as IL-6.[33] Out of a cohort of 619 patients with epithelial ovarian cancer, 192 were reported to have thrombocytosis that was also accompanied by increased IL-6 and thrombopoietin in the plasma.[33] Further research is warranted to determine the timing and duration of thrombocytosis in relation to the cancer progression.

Platelets, tumor proliferation, and low-dose aspirin.

The proliferation of cancer cells can be triggered by multiple mechanisms, including cancer cell interactions with platelets. One of the first observations that demonstrated the involvement of platelets in cancer cell proliferation was made in 1980 by Hara and colleagues.[43] The authors concluded that platelets contained “a survival and a mitogenic factor” that supported the proliferation response of a variety of cancer cells. Today, we know that platelet-induced cancer cell proliferation and tumor growth is associated with the secretion of various growth factors from platelet α-granules, including PDGF, TGFβ, EGF and VEGF. Importantly, the type of cancer cell interacting with platelets is a key determinant of the signal required to induce the proliferation response. Conditioned media from lung cancer cells co-cultured with platelets contained high levels of EGF, which induced lung cancer cell proliferation *in vitro*. Phospho-receptor tyrosine kinase array analysis identified phosphorylation of the EGF receptor and downstream signaling molecules as essential for lung cancer cell proliferation induced by the platelet secretome.[20] Inhibition of platelets with the $P2Y_{12}$ inhibitor clopidogrel was found to reduce EGF-induced lung tumor growth *in vivo*.[20] Secretome analysis of the media of breast cancer cells co-cultured with platelets revealed, compared to breast cancer cells grown without platelets, a striking increase of VEGF and PDGF, which promote progressive tumor growth by supporting the formation of new blood vessels and the proliferation of tumor cells, respectively.[22; 44] Further analysis found that inhibition of platelets with aspirin blocked platelet-induced angiogenesis *in vitro*. [22; 44; 45] Recently, our group has shown that PDGF released by platelets promotes pancreatic cancer cell proliferation by upregulating proliferative factors such as the oncoprotein c-MYC, a response that is reduced by targeting platelet activation with aspirin. [21] In addition, platelet-induced cancer cell proliferation is often associated with TGFβ-mediated pathways. Treatment with inhibitors of TGFβ signaling blocked platelet-induced

breast and hepatocellular carcinoma growth *in vitro*.[19; 46] In hepatocellular carcinoma cells, the proliferative effect of platelet TGFβ is dependent on Krupper-like factor 6, a transcription factor involved in tumor growth.[46] Thus, it is evident that the composition of the platelet secretome plays an important role in not only promoting cancer metastasis but also maintaining the proliferation ability of the tumor. These studies demonstrate the need for further investigations of the platelet secretome as a target to regulate cancer proliferation and growth.

Retrospective clinical studies have explored the anti-metastatic effect of aspirin, specifically in relationship to its anti-platelet therapeutic activity at low doses (75–100 mg/day).[3] Aspirin, via inhibition of the enzymes cyclooxygenase 1 (COX-1) and COX-2, prevents the synthesis and release of prostanoids, including the autocrine platelet agonist thromboxane A2 (TXA_2). At low doses (75–100 mg/day), aspirin predominantly targets COX-1 activity in platelets, whereas at higher doses (325–1,200 mg/day), it exerts anti-inflammatory properties by attenuating the activity of both COX-1 and COX-2.[47; 48] Several studies have demonstrated that aspirin reduces tumor growth, angiogenesis and metastasis, but whether this is an anti-platelet effect, an anti-inflammatory effect independent of TXA_2 formation, or both is still under investigation. Recently, aspirin has been proposed to inhibit angiogenesis through inhibition of platelet COX-1-dependent production of arachidonic acid (AA)-derived eicosanoids, particularly 15(S)-hydroxyeicosatetraenoic acid (15(S)-HETE).[49] Moreover, aspirin also seems to attenuate platelet secretion, thereby diminishing the release of growth factors known to facilitate dialogue between platelets and cancer cells.[47] Thus far, investigations of the effect of low-dose aspirin on the platelet secretome profile in response to cancer cells have been limited. Notably, three clinical studies have shown that aspirin can indirectly exert a protective effect against cardiovascular diseases by modulating platelet secretion.[50–52] Using proteomic approaches, Coppinger and colleagues showed that low-dose aspirin significantly reduced the release of growth factors and cytokines from platelets activated with collagen and ADP.

Defining the effects of low-dose aspirin on growth factor release by platelets in response to cancer cells and identifying concomitant changes in pro-growth signaling in cancer cells will be a challenge, given the complexity and heterogeneity of platelet-cancer interactions. In our previous studies, low-dose aspirin reduced colon and pancreatic cell proliferation induced by the platelet secretome yet was unable to inhibit prostate cancer cell-induced platelet secretion.[8; 21] These results suggest that effects of aspirin are dependent on the type of cancer, and therefore the use of aspirin therapy should be tailored to both the tumor type and the specific signaling networks and secretion responses activated in platelets by select types of tumors. The use of metabolic labelling of proteins and advanced proteomic and computational techniques holds promise to facilitate identification of the set of platelet-released proteins that are important for proliferation of a given cancer cell type and define the effect of aspirin on this protein signature. This will open up new research avenues into to the anti-cancer mechanisms of aspirin and provide a mechanistic understanding of the dialogue between platelets and specific tumor types.

The clinical history of aspirin in cancer therapy and current recommendations.

Beginning in the early 1980s, animal studies of chemical-induced carcinogenesis showed a protective effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on colon tumors.[53; 54] While the mechanism was unclear, the inhibition of cyclooxygenase was presumed to play a role. Due to the similar and permanent effects of low-dose aspirin on the cyclooxygenase enzyme, several epidemiologic trials were conducted to look for a benefit of aspirin on colorectal cancer in humans.[55–57] While the initial results of smaller trials were mixed, in 1991, the Cancer Prevention Study II of over 660,000 patients reported a 40% reduction in colon cancer mortality associated with the regular use of aspirin, with the benefit seen in both men and women.[57] Despite its large size, the retrospective nature of the trial and its dependence on lifestyle questionnaires limited its conclusions to evidence of association rather than causation.

Twelve years later, two randomized trials jointly published in the New England Journal of Medicine showed a clear benefit from low-dose aspirin for the secondary prevention of colorectal cancer.[58; 59] The relative risk for cancer recurrence was reduced by 20–35% within the first 12 months of the study. The benefits of aspirin were further verified in an editorial accompanying the research article.[60] However, since both trials used patients with a history of colorectal cancer or adenomas, the question of primary cancer prevention remained open. In the following decade, large randomized trials that had been designed to study aspirin for cardiovascular (CVD) benefit were reexamined to look for signals of cancer benefit.[61–63] The incidence of colorectal cancer in these trials was small, and findings of a benefit from aspirin were inconsistent. An analysis and recommendation from the United States Preventive Services Taskforce (USPSTF) in 2007 subsequently recommended against the routine use of aspirin for cancer prevention.[64] However, a 2010 meta-analysis of five of the largest prospective trials of aspirin showed a clear benefit for aspirin in reducing cancer incidence and mortality.[5] Unlike in secondary prevention, the benefits in primary prevention took over 5 years to manifest and were modest. Two additional meta-analyses that expanded the number of trials followed in 2012, strengthening the findings of benefit and better defining the time course and magnitude of benefit.[3; 4] In 2016, the USPSTF used these meta-analyses and their own analysis to recommended that many adults between the ages of 50 and 69 years of age would benefit from the use of aspirin for cancer prevention.[65] Despite the USPSTF recommendation, controversy exists regarding the role of aspirin for cancer prevention.

The absolute benefit in patients without a history of cancer is small and offset by the increased risk of serious bleeding. In the USPSTF analysis, cancer benefit alone is insufficient to recommend the initiation of aspirin therapy. However, in patients with sufficient CVD risk between the ages of 50 and 69 years, approximately 15 cases of colorectal cancer would be prevented for every 1000 patients treated for at least 10 years.[65] The incidence of major bleeds would be approximately 25 per 1000, with 2–3 of those being an intracranial hemorrhage. Thus, there is cautious optimism on the clinical utility of aspirin in cancer adjuvant therapy.

Optimizing the clinical use of aspirin will depend on careful patient selection. As the mechanism of aspirin for cancer prevention becomes better understood, future biomarkers may offer the possibility of selecting patients more likely the benefit.[21; 66] Ongoing clinical trials will also be useful. The Study to Assess the Efficacy and Safety of Acetylsalicylic Acid (ARRIVE; NCT00501059) was completed in 2017, and results will be available soon. One secondary endpoint in ARRIVE was time to the first occurrence of colon cancer. The Aspirin in Reducing Events in the Elderly trial (ASPREE; NCT01038583) is tracking fatal and non-fatal cancer incidence among nearly 19,000 enrolled patients and is expected to be completed in 2018.[67]

The epidemiology of low-dose aspirin for cancer therapy.

Low-dose aspirin use is common in the United States, with over 30% of the adult population routinely taking the drug.[68] While the majority of individuals take aspirin for primary and secondary prevention of cardiovascular disease, guidelines now endorse consideration of aspirin for colorectal cancer prevention in adults aged 50–59 who are not at increased risk for bleeding.[69] Despite the increase in bleeding events associated with routine aspirin use, microsimulation modeling has suggested a significant increase in quality adjusted life years gained by aspirin intake in this population.[69] While colorectal cancer incidences are decreasing due to the routine use of surveillance endoscopy, the disease remains the second most common cause of cancer related death in America, suggesting it to be an ideal target for preventative strategies.[70] The chemopreventive effects of aspirin have also been highlighted in certain familial cancer syndromes that predispose to colorectal cancer. Prospective trials have demonstrated a significant decrease in colorectal cancers associated with aspirin or celecoxib use in individuals with familial adenomatous polyposis [71; 72] and hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome).[73]

While colorectal cancer remains the most studied cancer with regard to aspirin chemoprevention, less robust data suggest the drug is effective at preventing other cancers. While prospective trials such as those confirming the benefit in colon cancer are lacking, meta-analysis of multiple aspirin-related clinical trials has suggested a decreased incidence in all cancers at 10 years of follow up (HR 0.88, 95% CI 0.80–0.98) as well as a decrease in all cancer-related mortality (HR 0.85, 95% CI 0.76–0.96).[4] Other small studies suggest aspirin may prevent esophageal cancer,[74] gastric cancer,[75] breast cancer,[76] and prostate cancer.[77] Unlike with colorectal cancer, large trials have yet to confirm these findings in other cancer types. Data on the use of aspirin during curative or palliative therapy for cancer are also lacking and currently inadequate to draw any strong conclusions.[78]

Lastly, aspirin also plays a significant role in patients with myeloproliferative neoplasms for primary prevention of thromboembolic events. Individuals with polycythemia vera, for instance, carry a significant risk of thrombotic events that has been shown in large trials to be effectively mitigated with aspirin.[79] This has led to routine aspirin use in the majority of patients with myeloproliferative neoplasms.

Concluding remarks.

Platelets are now considered an integral part of tumor progression. It is evident that secreted factors derived from both cancer cells and platelets play a crucial role in platelet-cancer cell communication and promote a microenvironment favorable to cancer progression. In a clinical setting, preoperative thrombocytosis is associated with cancer and indicative of a worse prognosis. The effectiveness of anti-platelet doses of aspirin in impairing cancer cell proliferation *in vitro* and reducing colon cancer metastasis and incidence in clinical studies provide further evidence of platelet-cancer cell crosstalk. Given the importance of platelet-derived growth factors in promoting cancer growth and metastasis, further characterization of tumor type-specific mechanisms leading to platelet secretion and tumor type-specific protein patterns in the platelet secretome could prove useful in cancer prognosis and the generation of new therapeutic targets.

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