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Aspirin limits platelet TXA2-mediated suppression of T-cell immunity to prevent cancer metastasis

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Abstract

Aspirin, a widely used non-steroidal anti-inflammatory drug, has shown promise in cancer prevention and reducing metastatic progression. This medication limits platelet thromboxane A2 (TXA2)-mediated suppression of T-cell immunity, thereby preventing cancer metastasis. Platelets, beyond their role in hemostasis, actively contribute to tumor progression and metastasis by various mechanisms, including shielding circulating tumor cells from immune surveillance and promoting their extravasation. One critical pathway involves platelet-derived TXA2, a potent lipid mediator that can directly suppress anti-tumor T-cell responses. TXA2 promotes immune evasion by inhibiting T-cell activation and proliferation, thus hindering the body's ability to effectively eliminate cancerous cells. Aspirin's well-known inhibitory effect on cyclooxygenase-1 (COX-1) is key here, as COX-1 is responsible for TXA2 synthesis in platelets. By irreversibly acetylating COX-1, aspirin effectively reduces TXA2 production. Then, the reduction in platelet TXA2 alleviates its immunosuppressive effects on T-cells, thereby restoring and enhancing anti-tumor immunity. The enhanced T-cell activity can then more effectively target and destroy circulating tumor cells, finally limiting the formation of secondary tumors and preventing metastasis.

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Introduction

Metastasis, the spread of cancer cells from primary tumors to distant organs, is responsible for 90% of cancer deaths globally (1). Despite advancements in primary cancer treatment, many patients with early-stage cancers experience metastatic recurrence due to the growth of micrometastases. These micrometastasis, however, are particularly vulnerable to immune attack; since, they are initially deprived of the immunosuppressive microenvironment found in established tumors. This vulnerability presents a unique therapeutic opportunity to exploit the immune system to prevent recurrence in early-stage cancer patients at risk of metastasis (2). Previous studies, have consistently observed that individuals with cancer who take daily low-dose aspirin experience a reduction in the spread of certain cancers, including breast, bowel, and prostate cancers (3). The recent meta-analyses of randomized controlled trials by Elwood et al have confirmed that aspirin treatment is associated with a reduction in metastasis in cancer patients (4). In colorectal cancer, the previous study by Reimers et al demonstrated that the association between aspirin administration and improved survival appears to be confined to tumors expressing high levels of human leukocyte antigen (HLA) class I, suggesting an immune-mediated effect (5). This study found that post-diagnosis aspirin use improved survival specifically in colon cancer patients whose tumors expressed HLA class I (5).

Recently, attentions directed toward platelets, as active participants in the tumor microenvironment and the metastatic

Key point

Metastasis causes 90% of cancer deaths by allowing cancer cells to disseminate from primary tumors to distant organs like lungs and liver. Disseminated micrometastases making them susceptible to immune surveillance, particularly by T cells. Aspirin has been identified as a significant factor in preventing cancer metastasis by mitigating the suppression of T-cell immunity mediated by platelet thromboxane A2. Recent findings detected that low-dose aspirin is associated with reduced cancer mortality and metastasis. This mechanism involves aspirin boosting T-cell immunity, thereby preserving effective T-cell responses against metastasizing cancer cells. it has been detected that blocking platelet derived thromboxane A2 (TXA2) by aspirin could be mediated through a T cell intrinsic ARHGEF1 dependent pathway. Thereby by inhibiting platelet cyclooxygenase-1 (COX-1) and lowering TXA2, low dose aspirin releases T cells to attack disseminated cancer cells and thereby reduces metastatic seeding in preclinical models.

cascade (6). Following shedding of circulating tumor cells from primary or secondary tumors, platelets are rapidly recruited to circulating tumor cells, forming a physical cloak around them. This cloak serves multiple pro-metastatic functions; since, it shields circulating tumor cells from natural killer (NK) cell-mediated lysis by masking surface ligands, provides adhesive molecules facilitating arrest on the endothelial lining of distant vessels, and releases growth factors and cytokines that promote tumor cell survival, extravasation, and seeding at secondary sites (7). Crucially, this platelet-tumor cell interaction is not merely physical; it involves potent biochemical signaling, with thromboxane A2 (TXA2) playing a starring role (8). Meanwhile, TXA2 is synthesized predominantly in platelets by the COX-1 pathway upon activation (9). It is a potent vasoconstrictor and the most powerful endogenous platelet activator and aggregator known, acting in an autocrine and paracrine manner through its G-protein coupled receptor (TP receptor) (10). The role of thrombosis is well-established; however, its immunomodulatory functions, particularly in cancer, are increasingly appreciated (11). Platelet-derived TXA2, released in the vicinity of circulating tumor cells and within the forming metastatic niche, exerts significant suppressive effects on adaptive immunity, specifically CD8+ cytotoxic T lymphocytes, as the primary immune cells responsible for recognizing and destroying cancer cells. This suppression occurs through several interconnected mechanisms (12). TXA2 signaling by TP receptors on T-cells can directly inhibit T-cell receptor signaling pathways (13). Engagement of TP receptors triggers intracellular cascades involving Gαq proteins, leading to increased intracellular calcium and activation of protein kinase C isoforms (14-16). This condition can interfere with the precise spatial and temporal organization of signaling molecules at the immunological synapse as the critical interface between a T-cell and its target dampening activation signals like calcium flux, NFAT (nuclear factor of activated T cells) nuclear translocation, and eventually, cytokine production and cytotoxic granule release (14-17). Furthermore, TXA2 promotes an immunosuppressive microenvironment; since, it can upregulate the expression of immune checkpoint molecules like PD-1 on T-cells and PD-L1 on tumor cells and myeloid-derived suppressor cells, facilitating T-cell exhaustion (18). TXA2 also stimulates platelets and other cells to release additional immunosuppressive factors such as transforming growth factor-beta (TGF-β) and prostaglandin E2 (PGE2), creating a milieu that actively inhibits T-cell proliferation, function, and survival while promoting regulatory T-cell (Treg) activity (18). The net effect is a significant impairment of the body's ability to mount an effective T-cell response against disseminating tumor cells, allowing them to evade immune destruction during their vulnerable transit and initial colonization phases. Aspirin (acetylsalicylic acid) uniquely disrupts the pro-metastatic-immunosuppressive axis at its source named platelet TXA2 generation (13). Its mechanism hinges on the irreversible acetylation of a specific serine residue (Ser529) within the cyclooxygenase active site of COX-1 (13,19). As platelets, being anucleate fragments and cannot synthesize new COX-1 enzyme; therefore, a single, low-dose of aspirin effectively shuts down TXA2 production in the entire circulating platelet pool for their lifespan (20). Additionally, aspirin inhibits COX-2; nevertheless, its effect on platelet COX-1 is dominant at low-doses due to the unique sensitivity and irreversibility of this inhibition in platelets (20). By blocking platelet COX-1, aspirin dramatically reduces systemic TXA2 levels. As a result, the consequence for anti-tumor immunity is profound. Several studies found that by diminished TXA2 signaling, the T-cell receptor signaling in CD8+ T-cells is restored, enhancing their activation, proliferation, and effector functions like IFN-γ production and tumor cell killing (13). Then, the immunosuppressive pressure on T-cells is lifted; expression of exhaustion markers like PD-1 decreases, and the inhibitory effects of TGF-β and other factors are mitigated (13). The metastatic niche becomes less hospitable to tumor cell survival and growth due to reduced platelet activation and the associated release of pro-angiogenic and pro-invasive factors (21). Moreover, aspirin dismantles the platelet-derived shield that protects circulating tumor cells not only physically but also immunologically, exposing them to vigilant T-cell surveillance (13). This mini-review sought to demonstrate how aspirin limits platelet TXA2-mediated suppression of T-cell immunity to prevent cancer metastasis.

Search strategy

In preparing this narrative mini-review, a comprehensive literature search was undertaken across several major databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. The search employed a range of pertinent keywords such as 'aspirin', 'thromboxane A2', and 'cancer' to ensure broad coverage of relevant studies.

Dual anticancer mechanisms through inflammation and immunity

Following inhibiting platelet activation, aspirin disrupts a pro-inflammatory cascade where platelet-derived factors induce COX-2 expression in the tumor microenvironment, promoting proliferation, angiogenesis, and inhibiting apoptosis (22). Moreover, aspirin preserves T-cell immunity by blocking TXA2-mediated ARHGEF1 activation (22). In the tumor microenvironment, persistently activated platelets release TXA2 and other mediators that; i) Stimulate stromal and epithelial cells to upregulate COX-2 and PGE2 pathways, driving carcinogenesis (18,23); ii) Bind to TXA2 receptors on T cells, activating ARHGEF1 and suppressing cytotoxic function (13); and iii) Create an immunosuppressive niche where neoantigen-expressing tumor cells evade immune detection (18). Hence, aspirin interrupts this vicious cycle at its source by irreversibly inhibiting platelet COX-1, thereby preventing TXA2 production and its downstream immunosuppressive effects. This condition allows T cells to recognize tumor neoantigens and eliminate micrometastases before they establish clinically detectable disease (13).

A short look at the guanine exchange factor ARHGEF1

At the molecular level, TXA2 engages a pathway in T cells that depends on the guanine exchange factor ARHGEF1. Activation of ARHGEF1 downstream of TXA2 suppresses proximal TCR signaling and reduces T-cell polyfunctionality (13). Conditional deletion of ARHGEF1 in T cells increases T-cell activation within metastatic niches and provokes immune-mediated rejection of lung and liver metastases in mouse models, directly linking the TXA2→ARHGEF1 axis to impaired anti-tumour immunity. These genetic data establish ARHGEF1 as a T-cell intrinsic immune checkpoint that is engaged by platelet signals (13). Aspirin and other selective COX-1 inhibitors reduce the availability of TXA2 by irreversibly acetylating platelet COX-1, thereby preventing TXA2 synthesis during the platelet lifespan (24). In experimental metastasis assays, aspirin treatment or platelet-specific COX-1 deletion lowered metastatic burden in a manner that required T-cell ARHGEF1 signaling, indicating that the anti-metastatic effect is immune-mediated rather than solely due to altered hemostasis or tumour cell biology. These findings provide a coherent mechanistic explanation for epidemiologic associations between low-dose aspirin administration and reduced cancer mortality or metastasis risk (13). The Key opportunities of this finding include repurposing low-dose aspirin as an adjuvant strategy to enhance immune control of micro-metastasis in early-stage cancer, and targeting the TXA2–ARHGEF1 pathway to develop more selective immunomodulatory agents (13). Beyond the immediate TXA2–ARHGEF1 axis, platelet activation appears to influence carcinogenesis through multiple, potentially synergistic routes. Platelet-derived mediators can induce COX-2 expression and PGE2 production in stromal and epithelial cells, fostering a pro-tumorigenic milieu characterized by enhanced proliferation, reduced apoptosis, angiogenesis, and increased motility (25). Thus, platelet COX-1 activity may amplify local inflammatory circuits that promote early tumor development as well as later metastatic progression. This dual role helps reconcile epidemiologic observations that both low-dose aspirin and selective COX-2 inhibitors can reduce adenoma formation and colorectal cancer risk (26); platelet inhibition curtails a feed-forward loop that otherwise elevates COX-2–dependent tumorigenic signaling in the tissue microenvironment (27).

Conclusion

Recent evidence positions aspirin as a multifaceted agent in cancer metastasis prevention, extending beyond its classic anti-thrombotic role. Central to this is its irreversible inhibition of platelet COX-1, profoundly suppressing TXA2 production. Platelet-derived TXA2 is now recognized as a significant immunosuppressive mediator within the tumor microenvironment and circulation. It directly impairs cytotoxic T-lymphocyte function by hindering their activation, proliferation, and tumor-cell killing capacity. The TXA2-mediated T-cell suppression creates a permissive niche for circulating tumor cells to evade immune surveillance and establish metastatic colonies. By effectively silencing the platelet-TXA2 axis, aspirin restores robust T-cell immunity. Then, unleashed cytotoxic T-lymphocyte can better recognize and eliminate disseminating cancer cells before they engraft at distant sites. This immunomodulatory mechanism, working in concert with aspirin's anti-platelet and anti-inflammatory effects, provides a compelling biological rationale for its observed association with reduced metastasis and improved cancer outcomes in epidemiological and some interventional studies.

Authors' contribution

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Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently,

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