Understanding How Aspirin Prevents Metastasis

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The effects of aspirin on cancer metastasis were first recognised over 50 years ago (1).[x] In a seminal study, Gasic and colleagues showed that fewer lung metastases developed in mice whose drinking water was supplemented with aspirin compared with control mice. Epidemiological data support the hypothesis that aspirin prevents cancer (2),[x] but the design and interpretation of randomized trials has been hampered by a lack of mechanistic understanding.

This is changing. In a recent report, Yang and colleagues describe a novel immunosuppressive mechanism which prevents T cells from eliminating cancer metastases (3). At the heart of this pro-metastatic mechanism is a protein called ARHGEF1 in T-cells that is activated by thromboxane A_2, a metabolite of the arachidonic pathway, which is inhibited by aspirin through inactivation of cyclooxygenase (COX) enzymes.

Building upon a large *in vivo* mouse genetic screen to identify host regulators of cancer metastasis Yang et al. focussed on ARHGEF1, one of 15 genes whose disruption in host tissues decreased the frequency of metastasis. Conditional mouse genetic experiments revealed that abrogating ARHGEF1 function in T cells was responsible for the effect on metastases (3). The search for upstream receptors driving the immunosuppressive function of ARHGEF1 led to the thromboxane A_2 receptor on T-cells. Administration of the thromboxane A_2 analogue U46619 increased metastasis in mice models, while aspirin in the drinking water, at pharmacologically relevant doses, reduced metastasis in control animals but not in those with a conditional deletion of

ARHGEF1 in T cells. This led to the conclusion that the anti-metastatic effects of aspirin are mediated by T cells through ARHGEF1 and provides, for the first time, a clear link between the known pharmacological effects of low-dose daily aspirin and cancer elimination.

The study by Yang et al. reinforces the hypothesis that platelets are key to understanding the anti-cancer effects of aspirin (Figure 1). The anti-cancer effects of aspirin are seen with low dose (75-100 mg) once daily administration, and the pharmacological target, the permanent inactivation of COX-1 in platelets, is well-established. Platelets have no nucleus and therefore cannot resynthesize COX enzymes hence the suppressive effect of aspirin on the synthesis of thromboxane A_2 lasts for about ten days -- the lifespan of the platelet. The analgesic/anti-inflammatory effects of aspirin are mediated through inhibition of COX-2 in systemic tissues requiring higher doses (300-600 mg) administered up to four times a day.

Further evidence that platelets are central to mediating the anti-cancer effects of aspirin is derived from studies on mice genetically depleted of functional COX-1 in platelets/megakaryocytes and therefore a model of the effects of once daily low-dose aspirin (4). Crossing these mice with $Apc^{Min/+}$ mice, a model of intestinal tumorigenesis, results in animals that develop fewer and smaller adenomas than $Apc^{Min/+}$ controls, demonstrating the importance of platelet COX-1 in early tumorigenesis. Furthermore, adenomas from the $Apc^{Min/+}$ COX-1-deficient mice express less COX-2 than $Apc^{Min/+}$ controls, suggesting that platelet COX-1 directly regulates COX-2 expression in adenomas which has a known role in carcinogenesis. This provides an explanation of how both low-dose aspirin and agents that inhibit COX-2 can prevent adenomas.

Platelets therefore appear to potentiate cancer development by promoting inflammation-driven COX-2 dependent carcinogenesis and by suppressing T cells from clearing metastases (Figure 1).

The link between aspirin and the immune system has further ramifications. It suggests that immunogenic tumours will respond to aspirin and indeed long-term randomised data shows aspirin prevents the highly immunogenic mismatch repair-deficient cancers in Lynch Syndrome (5). It also suggests that immune markers could predict aspirin response. In a large cohort study evaluating aspirin use after colorectal cancer resection HLA class I expression in the primary tumour was associated with improved overall survival in patients treated with aspirin (6).

Recent clinical trial results have confirmed that persons with *PIK3CA* variants in rectal and colorectal cancer tumours benefit from 3 years of once daily low dose aspirin when initiated within three months of surgery (time to recurrence hazard ratio 0.49 (0.24-0.98) (7). The link between PIK3CA variants and ARHGEF1 is not yet explained but potential explanations include the observation that PIK3CA mutations generate a public neoantigen or alternatively that PIK3CA mutations have an immunomodulatory effect on T cells similar to effects proposed for the MYC oncogene.

Yang et al. have provided an explanation for a phenomenon first reported over 50 years ago, by describing how daily low-dose aspirin can prevent metastases. Their results highlight both challenges and opportunities of drug repurposing. Aspirin is a low-cost generic drug, and cancer incidence is increasing particularly in low-and-middle income countries where there is a pressing need for affordable therapeutics. However, with no pharmaceutical company poised to extend the licence this may limit

prescribing in both the primary prevention setting and for the prevention of metastases. The study by Yang and colleagues however illustrates how improvements in technology and biological knowledge will allow the potential of older drugs to be realised.

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Figure 1

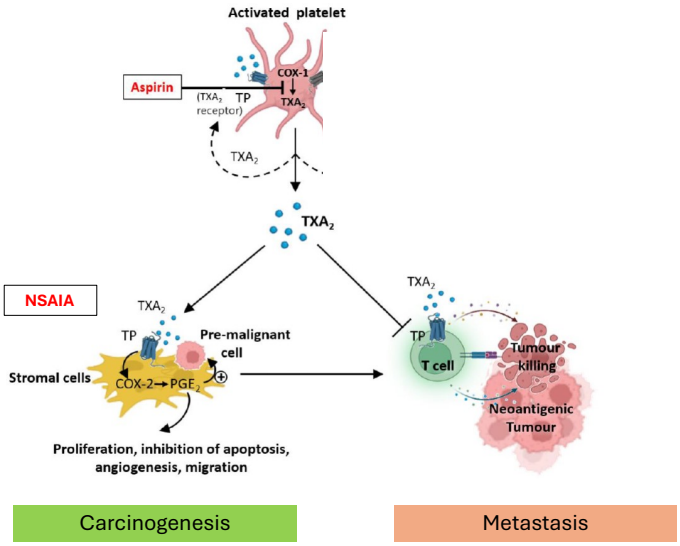

Figure 1. Inhibiting Platelet Activation Explains the Anti-Cancer effects of Aspirin.

Model of mechanism underlying the prevention of carcinogenesis and metastasis by aspirin and other cyclo-oxygenase inhibitors. In the tumor microenvironment, activated platelets release thromboxane A2 (TXA2), which interacts with receptors on stromal cells and immune cells. TXA2 promotes carcinogenesis by upregulating COX-2 and prostaglandin E2 pathways in stromal cells, leading to increased proliferation, inhibition of apoptosis, enhanced angiogenesis, and migration of cancer cells. TXA2 also exerts immunosuppressive effects on T cells, inhibiting their cytotoxic activity and thereby contributing to the progression of neoantigenic tumours and facilitating cancer metastasis. Aspirin inhibits platelet activation.