

## CLINICAL IMPLICATIONS OF BASIC RESEARCH

## Understanding How Aspirin Prevents Metastasis

Ruth E. Langley, M.B., B.S., Ph.D.,<sup>1</sup> and John Burn, M.D.<sup>2</sup>

The effects of aspirin on cancer metastasis were first recognized more than 50 years ago.<sup>1</sup> In a seminal study, Gasic and colleagues found that fewer lung metastases developed in mice whose drinking water was supplemented with aspirin than in control mice.<sup>1</sup> Epidemiologic data support the hypothesis that aspirin prevents cancer,<sup>2</sup> but the design and interpretation of randomized trials have been hampered by a lack of mechanistic understanding.

This is changing. In a recent report, Yang and

colleagues<sup>3</sup> describe a previously unrecognized immunosuppressive mechanism that prevents T cells from eliminating cancer metastases. At the heart of this prometastatic mechanism is a protein called ARHGEF1, which is activated by thromboxane A2 (TXA2), a metabolite of the platelet arachidonic acid pathway (see Key Concepts). This pathway is inhibited by aspirin through inactivation of cyclooxygenase (COX) enzymes.

Building on an *in vivo* genetic screen in mice to identify host regulators of cancer metastasis,<sup>4</sup>

### KEY CONCEPTS

#### Arachidonic acid pathway

A pathway that involves the metabolism of arachidonic acid, a polyunsaturated fatty acid released from cell membranes by phospholipases on cellular activation. Arachidonic acid is converted by cytosolic prostaglandin H synthases, which have both cyclooxygenase (COX) and hydroperoxidase (HOX) activity, to unstable intermediates, prostaglandin G2 and prostaglandin H2, respectively. Prostaglandin H2 is converted by tissue-specific isomerases to five primary prostanoids: thromboxane A2, prostaglandin D2, prostaglandin E2, prostaglandin F2 $\alpha$ , and prostaglandin I2. These prostanoids activate specific cell-membrane receptors, through which they effect and affect many physiological and pathologic cellular responses. The COX pathways of arachidonic acid metabolism are targets of drugs such as nonsteroidal antiinflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA).

#### Neoantigen

A novel peptide that is derived from a somatic variant in a tumor cell and can be recognized as “nonself” by T cells. Neoantigens are tumor-specific and have not been encountered during thymic T-cell development and are therefore not subject to central tolerance.

#### Platelet activation

A process in which platelets transform morphologically and functionally in response to various stimuli. This process is amplified by agonists such as TXA2, adenosine diphosphate (ADP), and thrombin, which bind to receptors on the platelet surface. These receptors couple to intracellular signaling pathways that lead to a change in platelet shape and to secretion and amplification of platelet responses to ensure stable aggregation and thrombus formation. Platelet activation is a key component of the response to tissue injury, immune surveillance, and carcinogenesis.



An illustrated glossary is available at NEJM.org



Yang et al. focused on ARHGEF1, which is 1 of 15 genes whose disruption in host tissues decreases the frequency of metastasis. Conditional genetic experiments in mice have shown that preventing or abolishing the function of ARHGEF1 in T cells is responsible for the effect on metastases. The search for upstream receptors driving the immunosuppressive function of ARHGEF1 led the authors to investigate the TXA2 receptor on T cells. Administration of the TXA2 analogue U46619 increased the risk of metastasis in mice models, whereas aspirin in the drinking water, at pharmacologically relevant doses, reduced the risk of metastasis among control animals but not among those with a conditional deletion of ARHGEF1 in T cells. This finding led to the conclusion that the antimetastatic effects of aspirin are mediated by T cells through ARHGEF1 and provided, for the first time, a clear link between the known pharmacologic effects of low-dose daily aspirin use and cancer elimination.

The study by Yang et al. reinforces the hypothesis that platelet activation is key to understanding the anticancer effects of aspirin (Fig. 1). The anticancer effects of aspirin are seen with low-dose (75 to 100 mg) once-daily administration, and the pharmacologic target, the permanent inactivation of COX-1 in platelets, is well established. Platelets have no nucleus and therefore cannot resynthesize COX enzymes, so the suppressive effect of aspirin on the synthesis of TXA2 lasts for approximately 10 days — the life span of the platelet. The analgesic and anti-inflammatory effects of aspirin are mediated through inhibition of COX-2 in systemic tissues, which necessitates the use of higher doses (300 to 600 mg administered up to four times per day).

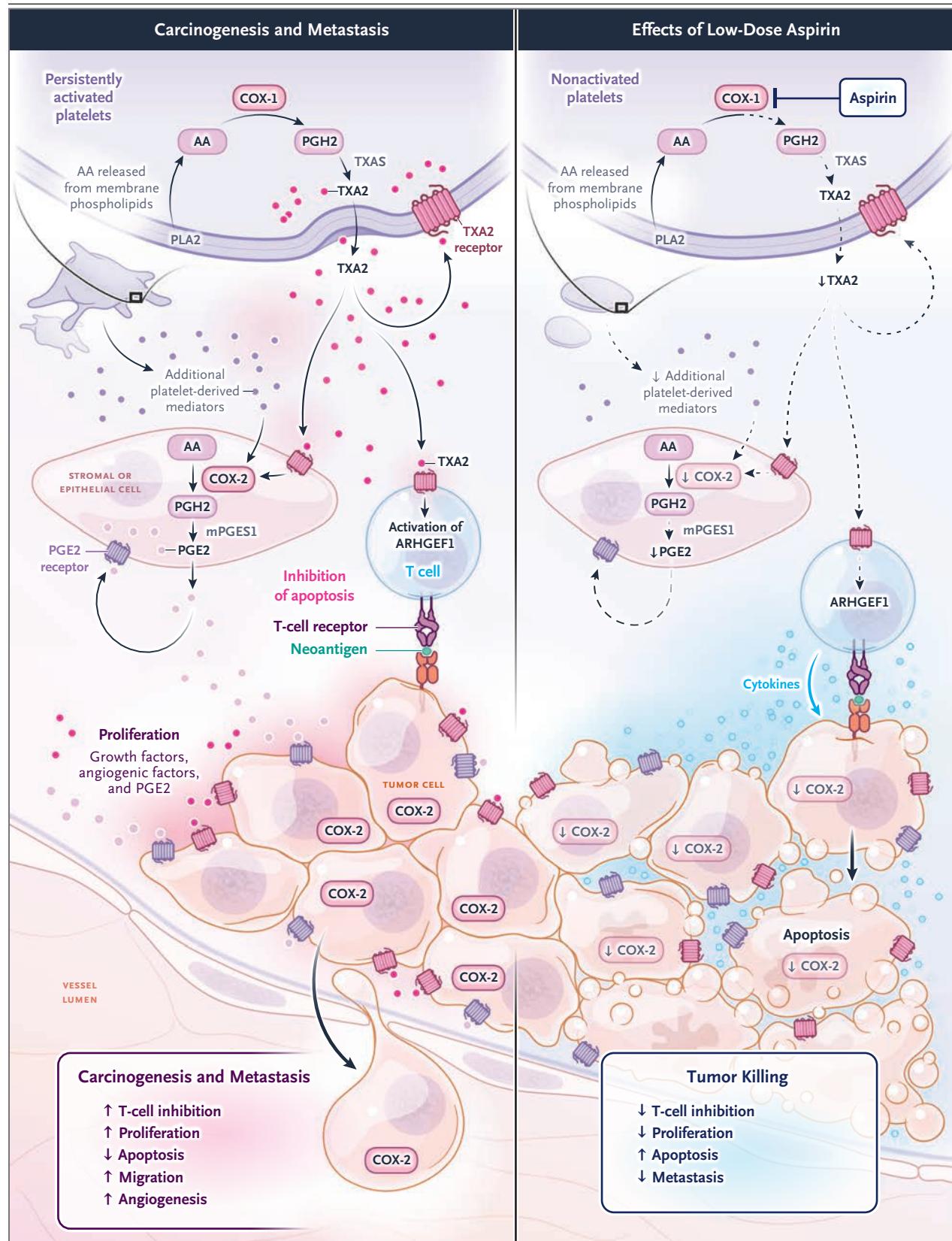
Further evidence that platelets are central to mediating the anticancer effects of aspirin is derived from studies in mice that are genetically depleted of functional COX-1 in platelets and megakaryocytes and that therefore serve as a model of the effects of once-daily low-dose aspirin use.<sup>5</sup> Crossing these mice with *Apc*<sup>Min/+</sup> mice, a model of intestinal tumorigenesis, results in progeny in which fewer and smaller adenomas develop than in *Apc*<sup>Min/+</sup> control mice — a finding that shows the importance of platelet COX-1 in early tumorigenesis. Furthermore, adenomas from the *Apc*<sup>Min/+</sup> COX-1-deficient mice express

less COX-2 than those from *Apc*<sup>Min/+</sup> controls, which suggests that a product of platelet COX-1 activity induces COX-2 expression in adenomas; COX-2 has a known role in carcinogenesis. These results provide an explanation of how both low-dose aspirin and agents that selectively inhibit COX-2 can prevent adenomas. Platelet activation therefore appears to potentiate cancer development and progression by promoting inflammation-driven COX-2-dependent carcinogenesis and by suppressing T cells from clearing metastases (Fig. 1).

The link between aspirin and the immune system has further ramifications. It suggests that immunogenic tumors will respond to aspirin therapy, and indeed, a long-term randomized trial has shown that aspirin prevents the highly immunogenic mismatch repair-deficient cancers in patients with the Lynch syndrome.<sup>6</sup> It also suggests that immune markers could predict response to aspirin therapy. In a large cohort study that evaluated aspirin use after resection of colorectal cancer, HLA class I expression in the primary tumor was associated with improved overall survival among patients treated with aspirin.<sup>7</sup>

Recent clinical trial results have confirmed that persons with *PIK3CA* mutations in rectal and colorectal cancer tumors benefit from 3 years of once-daily low-dose aspirin therapy when initiated within 3 months after surgery (hazard ratio for recurrence, 0.49; 95% confidence interval, 0.24 to 0.98).<sup>8</sup> The link between *PIK3CA* mutations 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 that is similar to effects proposed for the *MYC* oncogene.

By describing how daily low-dose aspirin use can prevent metastases, Yang et al. have provided an explanation for a phenomenon first reported more than 50 years ago. Their results highlight both the challenges and opportunities of drug repurposing. Aspirin is a low-cost generic drug, and the incidence of cancer 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 license,



**Figure 1 (facing page). Inhibition of Platelet Activation and the Anticancer Effects of Aspirin.**

Shown is a model of the mechanism underlying the prevention of carcinogenesis and metastasis by low-dose daily aspirin, which irreversibly inhibits platelet cyclooxygenase (COX)-1 and platelet activation. In the tumor microenvironment, activated platelets release thromboxane A2 (TXA2), which interacts with receptors on stromal cells and immune cells. TXA2 promotes carcinogenesis by up-regulating COX-2 and prostaglandin E2 (PGE2) pathways in stromal cells, which leads to increased proliferation, inhibition of apoptosis, enhanced angiogenesis, and migration of cancer cells. TXA2 also exerts immunosuppressive effects on T cells through a protein called ARHGEF1,<sup>3</sup> inhibiting their cytotoxic activity and thereby contributing to the progression of neoantigenic tumors and facilitating cancer metastasis. The mechanism by which PIK3CA mutations in cancer cells enhance sensitivity to aspirin is currently unknown. AA denotes arachidonic acid, mPGES1 microsomal prostaglandin E synthase 1, PGH2 prostaglandin H2, PLA2 phospholipase A2, and TXAS thromboxane A synthase.

prescribing aspirin in the context of primary prevention, as well as for the prevention of metastases, may be limited. We hope that the study by Yang and colleagues will prove to be an incentive for the redeployment of an older drug.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

<sup>1</sup>Medical Research Council Clinical Trials Unit, Institute of Clinical Trials and Methodology, University College London, London; <sup>2</sup>Newcastle University Translational and Clinical Research Institute, Newcastle upon Tyne, United Kingdom.

This article was updated on December 11, 2025, at NEJM.org.

1. Gasic GJ, Gasic TB, Murphy S. Anti-metastatic effect of aspirin. *Lancet* 1972;2:932-3.
2. Bosetti C, Santucci C, Gallus S, Martinetti M, La Vecchia C. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. *Ann Oncol* 2020; 31:558-68.
3. Yang J, Yamashita-Kanemaru Y, Morris BI, et al. Aspirin prevents metastasis by limiting platelet TXA<sub>2</sub> suppression of T cell immunity. *Nature* 2025;640:1052-61.
4. van der Weyden L, Arends MJ, Campbell AD, et al. Genomewide in vivo screen identifies novel host regulators of metastatic colonization. *Nature* 2017;541:233-6.
5. Bruno A, Contursi A, Tacconelli S, et al. The specific deletion of cyclooxygenase-1 in megakaryocytes/platelets reduces intestinal polyposis in *Apc<sup>Min/+</sup>* mice. *Pharmacol Res* 2022;185:106506.
6. Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. *Lancet* 2020; 395:1855-63.
7. Reimers MS, Bastiaannet E, Langley RE, et al. Expression of HLA class I antigen, aspirin use, and survival after a diagnosis of colon cancer. *JAMA Intern Med* 2014;174:732-9.
8. Martling A, Hed Myrberg I, Nilbert M, et al. Low-dose aspirin for PI3K-altered localized colorectal cancer. *N Engl J Med* 2025; 393:1051-64.

DOI: 10.1056/NEJMcb2502386

Copyright © 2025 Massachusetts Medical Society.

**APPLY FOR JOBS AT THE NEJM CAREERCENTER**

Physicians registered at the NEJM CareerCenter can apply for jobs electronically.

A personal account created when you register allows you to apply for positions, using your own cover letter and CV, and keep track of your job-application history.

Visit [nejmcareercenter.org](http://nejmcareercenter.org) for more information.