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Review Article

# Aspirin, platelets, and cancer: The point of view of the internist

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ABSTRACT

Growing evidence suggests the beneficial effect of aspirin against some types of cancer, particularly of the gastrointestinal tract, and it has been provided for an effect both in cancer prevention as well as in survival improvement of cancer patients. Aspirin benefits increase with duration of treatment, especially after 10 years of treatment. The inhibition of platelet activation at sites of gastrointestinal mucosal lesions could be the primary mechanism of action of low-dose aspirin. Indeed, the formation of tumor cell-induced platelet aggregates may favor immune evasion, by releasing angiogenic and growth factors, and also by promoting cancer cell dissemination. Moreover, platelets may contribute to aberrant COX-2 expression in colon carcinoma cells, thereby contributing to downregulation of oncosuppressor genes and upregulation of oncogenes, such as cyclin B1. Platelet adhesion to cancer cells leads also to an increased expression of genes involved in the EMT, such as the EMT-inducing transcription factors ZEB1 and TWIST1 and the mesenchymal marker vimentin. The aspirin-mediated inactivation of platelets may restore antitumor reactivity by blocking the release of paracrine lipid and protein mediators that induce COX-2 expression in adjacent nucleated cells at sites of mucosal injury. Thus, recent findings suggest interesting perspectives on "old" aspirin and NSAID treatment and/or "new" specific drugs to target the "evil" interactions between platelets an cancer for chemoprevention.



## 1. Introduction

Aspirin has a well-recognized role in the prevention of thrombotic cardiovascular diseases [1]. Guidelines for prophylactic aspirin use currently consider the cardiovascular benefits against the potential harm from aspirin-induced bleeding [2]. Recently, several papers suggest a chemopreventive effect of aspirin against some cancers, particularly of the gastrointestinal (GI) tract. In fact, daily aspirin use reduces the risk of colorectal cancer and recurrence of adenomatous polyps, during long-term follow-up, and recent evidence has been provided for an effect both in cancer prevention, as well as on survival of cancer patients [3,4]. In fact, secondary analyses of cardiovascular primary prevention trials showed that daily low-dose aspirin use could also reduce the incidence of all cancers combined. Thus, a reduction in the overall cancer incidence beginning during the first 10 years of treatment could tip the balance of benefits and risks favorably in populations with an average cardiovascular risk, in which uncertainty exists for the use of aspirin in primary prevention. Finally, it is under investigation the aspirin effect on age-related cognitive decline for dementia prevention [5].

Platelet function has been recognized to be a feature of occult cancer more than 60 years ago [6]. Platelets have been involved in the mechanisms leading to carcinogenesis, tumor growth, tumor angiogenesis, and tumor metastasis as well as in the modulation of tumor therapy (Fig. 1). Thus, increasing attention has been given to therapeutic changes in platelet number and function for cancer prevention or survival prolongation.

The mechanism by which aspirin may exert its activity is not completely clear. Different mechanisms of action have been suggested to explain the chemopreventive effect of aspirin, including acetylation of proteins of blood coagulation, and direct inhibition of the COX family of enzymes involved in prostaglandin synthesis. The COX-2 enzyme is strongly and rapidly induced in response to mediators of inflammation, and its expression correlates with increased cell proliferation and tumor promotion. COX-2 induction in human colon cancer cells by platelet-derived mediators has been documented [7]. Thus, aspirin can decrease the production of potentially neoplastic prostaglandins arising from COX-2-mediated catalysis of arachidonic acid. However, this may explain only a chemopreventive effect of high-dose aspirin [8], including the inhibition of COX-2 in the GI mucosa and its downstream effects on cellular proliferation, apoptosis, and angiogenesis. In fact, aspirin has a broader range of downstream effectors, such as NF-KB, as well as the inhibition of the Wnt signaling and of stem cell growth possibly as the result of enhanced beta-catenin phosphorylation [9]. However, the chemopreventive effect of aspirin is detectable at low doses (100 mg

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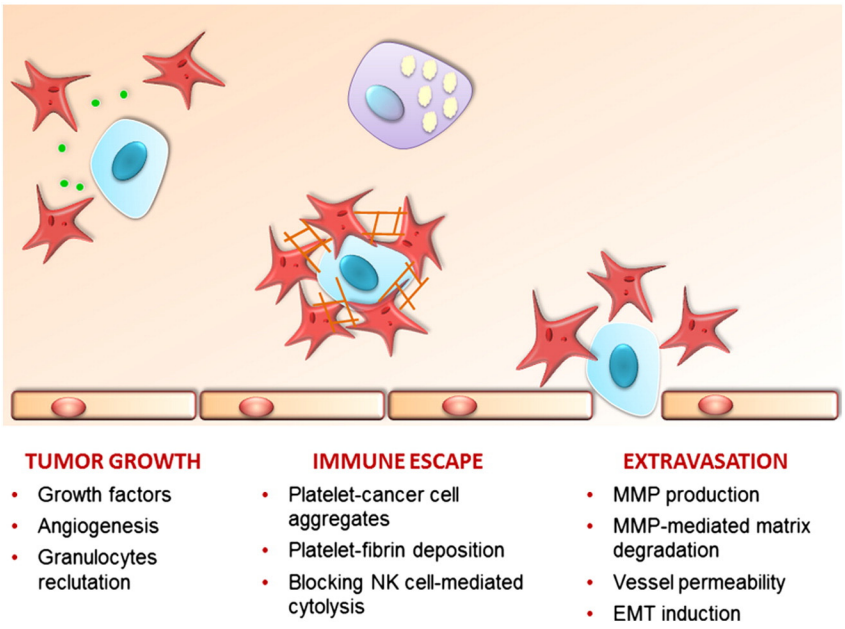


**Fig. 1.** Platelets can bind to cancer cells, thereby leading to platelet–cancer cell conjugates formation and fibrin deposition around cancer cells, thereby helping tumor cells to escape immune response. Platelets can also enhance cancer cell binding to endothelial cells through selectin-dependent tethering/rolling and integrin-dependent adhesion, and they may regulate endothelial permeability. Platelets are involved in basement membrane exposure, by enhancing matrix metalloproteinases (MMP)-mediated degradation of extracellular matrix. Finally, platelet may induce an endothelial-mesenchymal transition (EMT), thus leading to morphological change of cancer cells toward an invasive mesenchymal-like phenotype, with increased expression of mesenchymal makers, transcription factors and MMPs.

or less), and higher doses are not more effective than these doses [10]. Furthermore, the risk of developing colorectal cancer was also observed during long-term follow-up of healthy women treated with alternate-day 100 mg aspirin [11].

Whether we hypothesize a direct effect of aspirin on nucleated cellular targets (cancer or inflammatory cells), the chemopreventive effects of low-dose aspirin administered once daily do not fit with its pharmacokinetics (very short half-life) and pharmacodynamics (relatively the selective inhibition of platelet COX-1) [1]. Thus, Thun et al. hypothesized that the inhibition of platelet activation may mediate both the cardioprotective and cancer-preventive effects of low-dose aspirin [2]. For instance, during the early stages of colorectal carcinogenesis, the inhibition of thromboxane-dependent platelet activation at GI mucosal lesions could be the primary effect of low-dose aspirin, acting upstream of platelet-driven COX-2 expression in adjacent nucleated cells of the intestinal mucosa [1].

## 2. Role of aspirin in cancer prevention

Beyond atherothrombosis prevention, aspirin-mediated platelet inhibition has been related to venous thromboembolism prevention, reduced risk of dementia, and chemoprevention of colorectal and other cancers [1]. In a systematic review analyzing long-term follow-up of randomized trials of aspirin in prevention of vascular events, daily aspirin was shown to reduce the incidence of colorectal cancer [12]. A post hoc meta-analysis of four trials with 2967 randomly assigned participants demonstrated reduced risk of recurrence in aspirin treated subjects [13]. Indeed, adenomas were found in 424 of the 1156 participants allocated to placebo and in 507 of the 1542 participants allocated to any dose of aspirin [13]. Metastatic lesions were found in 12% of participants in the placebo group and in 9% of participants taking aspirin [13]. The long-term, continuous use of low-dose aspirin was associated with reduced colorectal cancer risk, and the adjusted odds ratios (OR) for colorectal cancer associated with ever use of low-dose aspirin was 1.03 [14]. Continuous long-term use (≥5 years) of low-dose aspirin was associated with a 27% reduction in colorectal cancer risk, whereas the overall OR for cumulative long-term use was close to 1.0 [14]. Moreover, Rothwell et al. demonstrated the even short-term daily aspirin can reduce cancer incidence and mortality [15]. Indeed, aspirin reduced cancer deaths, particularly from 3 years onwards, thus resulting in fewer non-vascular deaths overall [15].

The inhibition of platelet activation at sites of gastrointestinal mucosal lesions could be the primary mechanism of action of low-dose aspirin. Aspirin-mediated inactivation of platelets may restore antitumor reactivity by blocking the release of paracrine lipid and protein mediators that induce COX-2 expression in adjacent nucleated cells at sites of mucosal injury [16] (Fig. 2). In vivo aspirin inhibits thromboxane-mediated release of a tumor growth factor called sphingosine-1-phosphate (S-1P) from platelets [17].

Other possible effects of aspirin include acetylated-COX-2-dependent generation of aspirin-triggered lipoxins, which inhibit cell proliferation, transcription-mediated expression of COX-2, and attenuation of COX-2/peroxidase-mediated activation of carcinogens, such as polycyclic aromatic hydrocarbons [18,19]. Aspirin may induce acetylation of p53 in human colon cancer cells in a concentration-dependent manner [20], and the drug may acetylate recombinant p53 in vitro, thus suggesting that it occurs through a non-enzymatic chemical reaction [20]. Moreover, aspirin has been shown to decrease c-Myc protein levels in human HCT-116 colon and in other cancer cell lines, in a concentration-dependent manner. Aspirin taken up by cells is rapidly metabolized to salicylic acid, thus suggesting that aspirin's inhibitory effect on c-Myc may occur through formation of salicylic acid. Northern blot analysis showed that both aspirin and salicylic acid can decrease c-Myc mRNA levels. Further, pretreatment of cells with lactacystin, a proteasome inhibitor, partially prevented the downregulatory effect of both aspirin and salicylic acid, suggesting an involvement of 26S proteasomal pathway [21].

Recently, aspirin use has been investigated in relation to adjuvant and neoadjuvant therapies. In patients with stage II–III rectal cancer and candidates for chemoradiation (CRT), aspirin use was associated with a higher rate of tumor downstaging, and good pathological response [22]. Aspirin was also associated with a better 5-year

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