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Review

The anti-tumor effect of aspirin: What we know and what we expect

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ABSTRACT

Aspirin has been widely used as an antipyretic analgesic drug. More and more evidences have shown that aspirin may be play some role on anti-tumor. In this article, we reviewed the research history of aspirin in the treatment and prevention of cancer. Many epidemiological and clinical studies have shown that aspirin can reduce the risk of a variety of malignant tumors and reduce cancer mortality. In addition, we discuss the specific mechanisms of aspirin in the anti-tumor effects. It has been found that aspirin mainly depends on the COX pathway and non-COX pathway to inhibit tumor cell growth and to curb tumor development. In this article, clinical studies and anti-tumor mechanism studies published in recent years are reviewed.

Aspirin is a salicylic acid-based medicine. Because aspirin is inexpensive and does not require a prescription, it has been widely used. In the late 18th century, salicylic acid extracted from the willow tree was widely used as an analgesic and antipyretic medicine [1]. In 1897, aspirin was first synthesized and purified by Felix Hoffmann, who made aspirin one of the most famous medicines [1]. In 1904, the formulation of aspirin was changed from a powder to a tablet, which broadened its application [2]. In addition to being an analgesic and anti-inflammatory drug, aspirin has an important role in preventing cardiovascular disease [3]. Aspirin can reduce the risk of cardiovascular events, such as a heart attack and stroke [3]. In recent years, many clinical epidemiological studies have found that with an increase in aspirin intake, tumor mortality decreases exponentially in the colon, breast, lung, prostate and other organs of cancer patients [4]. As a result, more and more scholars believe that aspirin has an anti-tumor effect, with its specific anti-tumor mechanism involving the COX pathway and non-COX pathway. This article will mainly review two aspects of clinical research and the relevant mechanism.

1. Anti-tumor clinical studies of aspirin

As early as 1988, it was reported that aspirin can reduce the risk of colorectal cancer [5,6]. Later, during the study of rheumatoid arthritis and cardiovascular disease, researchers accidently found that aspirin can reduce the risk of colorectal cancer, in addition to its primary roles [7]. The WHS (Women's Health Study) and PFS (Physicians' Health Study) are two large-sample randomized trials. The results of these trials are also similar to the conclusion that aspirin can significantly reduce the incidence of colorectal cancer, especially proximal colorectal cancer. After an 18-year follow-up, it was found that the incidence of colorectal cancer was 20% less in subjects who received aspirin than in subjects who received placebo compared with 10-year follow-up observation data [8]. Through further study, the researchers gradually found that the anti-tumor effect of aspirin was not confined to colorectal cancer but extended to gastric cancer, breast cancer, ovarian cancer, liver cancer, prostate cancer, lung cancer and other tumor diseases [9–13]. Thus far, researchers have conducted meta-analyses of random trials and observation trials of the anti-tumor effect of aspirin and more powerfully demonstrated that aspirin can reduce overall cancer incidence from an evidence-based perspective. The analyses show that aspirin has an anti-tumor effect on many malignant tumors [14–16].

In the studies of the anti-tumor effect of aspirin, more and more evidence shows that long-term daily aspirin use has at least an anti-tumor effect. Rothwell et al., conducted meta-analyses of relevant papers on the anti-tumor effect of aspirin in 2010 and 2013 and found that a daily dose of aspirin for at least 5 years can significantly reduce overall cancer risk, and that the longer aspirin was taken, the better the effect of reducing the risk of cancer [17–19]. Since then, many studies have shown that under the condition of long-term daily aspirin use,

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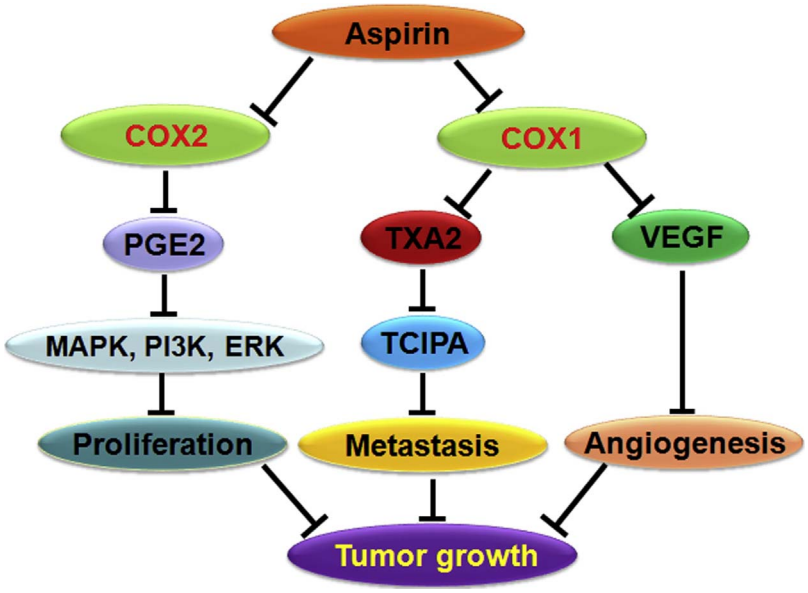

Fig. 1. Aspirin inhibits tumor growth through COX pathways. Firstly, aspirin can effectively inhibit COX-2 to reduce PGE2, which can promote tumor cell proliferation through multiple signaling pathways, including MAPK, PI3K, and ERK pathways. Secondly, aspirin causes platelet dysfunction and effectively inhibits platelet release by inhibiting COX-1, which can promote tumor metastasis by inducing TXA2 and TCIPA. At last, aspirin can inhibit COX-1 in platelets, resulting in a decline in the overall levels of serum VEGF to inhibit tumor angiogenesis.

aspirin can reduce cancer risk. In addition, studies of the anti-tumor effect of long-term daily use did not define the relationship between the dose of aspirin and the anti-tumor effect. At present, there is controversy about how many doses of aspirin have the best antitumor effect. Different studies used different dose settings. Based on the existing literature, it is found that low doses of aspirin were about 75 mg/d to 160 mg/d, standard doses of aspirin were about 160 mg/d to 300 mg/d, high doses of aspirin were about 300 mg/d to 325 mg/d [20–22]. Some scholars thought that low-dose aspirin had no anti-tumor effect but that standard- or high-dose aspirin has an anti-tumor effect [20–22]. Other scholars thought that low- and standard-dose aspirins have equal anti-tumor effects but that the anti-tumor effect of high-dose aspirin is stronger [23–25]. Similar to studies on the anti-tumor effect of aspirin, more and more primary and secondary studies show that low-dose aspirin clearly reduces the risk of cancer, especially colorectal tumors. Therefore, the conclusion that long-term daily low-dose aspirin use has an anti-tumor effect has been approved by most scholars. For example, the United States Preventative Services Task Force drafted a proposal that low-dose aspirin could be used for the primary prevention of colorectal cancer in aged patients who were at medium to high risk. However, the side effects of long-term use of aspirin, such as gastrointestinal bleeding, were concerning. Some scholars argued that through long-term aspirin use, the side effects of aspirin would be reduced to increase net benefits. This is mainly due to the reduction of the cancer risk by aspirin to lead to the conservation of medical resources and the protection for healthy people. However, all the studies of the anti-tumor effect of long-term aspirin taken every other day did not find a significant anti-tumor effect on tumors, especially colorectal cancer [26].

More and more studies now confirm that aspirin can reduce the morbidity and mortality of tumors, including bladder cancer, breast cancer, esophageal cancer, gastric cancer, colorectal cancer, liver cancer, lung cancer, and prostate cancer, among others. However, some issues with aspirin, including its dosage schedule (daily or every other day), amount (low dose or high dose) and side effects, such as gastrointestinal bleeding, remain to be further researched by scholars.

2. Anti-tumor mechanism of aspirin

2.1. Inhibition of COX to cause platelet-associated dysfunction

Cyclooxygenase (COX), known as prostaglandin oxidase reductase, has two types of isozymes, COX-1 and COX-2. COX-1 is constitutively expressed and COX-2 is strongly induced by pro-inflammatory stimuli. The former regulates vasomotion, platelet aggregation, gastric mucosal blood flow, gastric mucus secretion, and renal function, among other functions. The roles of COX-1 are related to the protection of gastrointestinal mucosa, regulation of platelet aggregation, regulation of peripheral vascular resistance and distribution of renal blood flow [27]. COX-2 is expressed in the vascular endothelium, brain, kidney and other organs. COX-2 also participates in the conversion of arachidonic acid to PGE2 in human myeloid cells and cancer tissues [28,29]. PGE2 can promote tumor cell proliferation and inhibit apoptosis through multiple signaling pathways, including MAPK, PI3K, ERK and cAMP/PK in lung cancer cells [29]. Aspirin can effectively inhibit COX-2 but not only in inflammatory pathologies and inhibit the proliferation of tumor cells through this pathways [30].

COX-1 is the only form of COX in platelets and is related to the synthesis of thromboxane A2 (TXA2) [31]. COX-1 plays a key role in platelet aggregation via TXA2 [31]. Research has shown that tumor cells depend on platelet aggregation to protect themselves from immune system monitoring; therefore, platelets play an important role in tumor cell metastasis [32]. This phenomenon is known as tumor cell-induced platelet aggregation (TCIPA) [32]. Platelet aggregation is a necessary mechanism for circulating tumor cells to escape immune system surveillance, promote their survival rates and migrate to a new microenvironment [33,34]. Aspirin can affect platelet aggregation and have an anti-tumor effect. Aspirin causes platelet dysfunction and effectively inhibits platelet release by COX-1. Then, irreversible inactivation of COX-1 is induced, which indirectly inhibits platelet aggregation. Finally, tumor cell metastasis is inhibited *in vitro* [35].

In the process of tumor growth, vessels can provide tumor cells with necessary nutrients. Therefore, the formation of vessels plays a very important role in tumor growth. The tumor formation process is determined by the balance of promoting angiogenesis factors and inhibiting angiogenesis factors [36]. Under normal physiological conditions, platelets release more than 30 promoting angiogenesis factors that promote wound healing [36]. Vascular endothelial growth factor (VEGF) is one of the most important angiogenesis factors, and more than 80% of VEGF in the whole circulation is released by platelets [36]. COX-1 is overexpressed in the platelets of tumor patients and causes platelet secretion of VEGF [37]. Aspirin can inhibit COX-1 in platelets, resulting in a decline in the overall levels of serum VEGF in mouse model [38]. The decrease in serum VEGF reduces the delivery of nutrients to tumors via angiogenesis and inhibits tumor growth [38,39] (Fig. 1).