Advances in antitumor effects of NSAIDs

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Abstract: In recent years, the reports on using nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer prevention and treatment have been on the rise. In 2017, the US Preventive Services Working Group issued primary prevention guidelines on the use of NSAIDs, especially aspirin, for cardiovascular disease and colorectal cancer, and formally established the role and status of aspirin in cancer prevention. However, the mechanism of NSAIDs on preventing cancer is still not clear. In this paper, the progress of the application of NSAIDs, especially aspirin, in the prevention and treatment of tumors in recent years is summarized, and new ideas and directions for the follow-up study are also discussed.

Keywords: NSAIDs, aspirin, platelets, cancer

Introduction

In 1897, German chemist Felix Hoffmann successfully applied salicylic acid and acetic anhydride to synthesize acetyl salicylic acid (acetylated salicylic acid) and obtained excellent effects in the treatment of rheumatoid arthritis for his father. This drug was named aspirin. Since then, this anti-inflammatory drug has been officially accepted in clinical practice, making it the most widely used antipyretic, analgesic and anti-inflammatory drug in the world. In addition to treatment, aspirin has been utilized as a standard preparation for the evaluation of other drugs. The molecular structure of aspirin is simple but used in vivo aspirin has shown a variety of effects over the years. It has been used as analgesic, antipyretic, anti-inflammatory and antirheumatic treatment in cardiovascular and cerebrovascular thrombosis. While its side effects cannot be ignored, especially long-term use of aspirin can lead to increased risk of gastrointestinal bleeding, increased uric acid, allergic asthma, coagulation inhibition amongst others.¹

In recent years, different types of NSAIDs have been developed and applied to clinical treatment, but among all NSAIDs, aspirin still seems to be the best and first choice.²

Some large epidemiological studies have displayed that aspirin shows great effect in the primary and secondary prevention of cancer and in a variety of malignant tumor treatments (especially in colon cancer, stomach cancer etc.).³⁻⁶ In May 2009, a meta-analysis of aspirin in the prevention of colorectal cancer (CRC) and other cancers in recent years reports that regular administration of aspirin is associated with the reduction of the incidence of cancer. This attracted scientific interest and posed the question: could anti-inflammatory drugs be used for the prevention and treatment of the tumor? There are some problems raised in this hypothesis, such as how to avoid the
gastrointestinal bleeding caused by long-term use of aspirin and the optimal dosage of aspirin. Therefore using aspirin in cancer prevention and treatment is still very controversial. In 2012, Rothwell indicated that regular administration of aspirin (≥75 mg/daily) could reduce the incidence of adenocarcinoma, CRC, and lung cancer, inhibit tumor metastases, and improve the survival rate of cancer patients. Additionally, they hypothesized that aspirin could inhibit tumor metastasis by eliminating platelet aggregation.

Early theories indicated that anti-inflammatory drugs could remove inflammatory factors in the surrounding inflammatory microenvironment of the tumor, so that the tumor cells can be directly exposed to immune cells, and then immune cells can function through immune recognition to achieve the role of cleaning up tumor cells. It is known that the body can self-recover after short-term inflammatory response, and this is a normal body self-protection mechanism, but long-term chronic inflammation may lead to cancer. Colotta et al proposed that tumors are caused by inflammation factors (IL-1, IL-6, IL-12, IL-17, TNF-α, TGF-β, etc.) assembling and the reactive oxygen species (ROS) produced by inflammatory infiltrating cells in the inflammatory microenvironment causing DNA damage (such as P53 gene mutation) and further induce normal cell carcinogenesis. Based on this, Okada et al created gp91phox gene knockout mouse implanted with or without degenerated fibro sarcoma cells (QR cells) and wild-type mouse macrophages. Compared to the gene knockout mouse, mouse implanted with wild-type macrophages increased frequency of tumor development, and showed macrophage-driven ROS participated in the development of tumors. Amino guanidine is a broad inhibitor of inducible nitric oxide synthase, and its regulation can partially and significantly inhibit the transformation of degenerating QR cells into fibrosarcoma cells, therefore Futoshi Okada et al speculated that in addition to ROS there was nitrous oxide (NO) involved in the process of tumor deterioration. In addition, the inflammatory cytokines, chemokines (IL family) and NK cells can accumulate in the surrounding microenvironment of the tumor, and mediate the growth and metastasis of tumor cells (related to the upregulation of the expression of vascular growth factor in the surrounding tumor microenvironment). Additionally, the inflammatory factor and histamine can increase the permeability of the vessel wall and the lymphatic wall, and assist the distal metastasis of the tumor. This article was therefore regarded as the cornerstone of the researches.

**Aspirin used in primary tumor prevention**

A great number of large epidemiological studies found that long-term use of low-dose aspirin (75–300 mg/daily) can effectively inhibit a variety of cancer incidence, malignant cancer metastasis rate, and provide patients with a high survival rate. In 2012, Rothwell et al conducted a meta-analysis of the six trials of daily low-dose aspirin in primary prevention (35,535 participants) and pointed out that the regular administration of low-dose aspirin (75–300 mg/daily) for more than 3 years can reduce cancer risk by 24% (324 vs 421 cases; OR = 0.76, 95% CI 0.66–0.88, P=0.0003). In addition, the aspirin group reduced the risk of CRC within 20 years in six randomized trials and 26 case–control studies. At the same time, the risk of esophageal cancer, gastric cancer, cholangiocarcinoma and breast cancer in the aspirin group was significantly decreased. Rothwell et al analyzed five large randomized clinical trials which examined the effects of aspirin (75 mg/daily or more) on tumors. The results of the analysis showed that aspirin could reduce the incidence of distant metastases by 36% and reduce the risk of cancer-specific mortality by 50% compared with the control group. For patients with adenocarcinoma, the risk of morbidity can be reduced by 46%. In patients with no metastatic adenocarcinoma at the time of initial diagnosis, the use of aspirin in the subsequent long-term observation can reduce the associated cancer metastasis rate by 70%. In 2014, Cuzick et al also concluded that taking low doses of aspirin (30–100 mg/daily) for 10 years can reduce the risks of gastric cancer, esophageal cancer, and CRC by 30%. Liao et al found regular use of aspirin (twice a week or more, standard dose of 325 mg aspirin tablets) after diagnosis, compared with wild-type PIK3CA cancer patients, mutant PIK3CA CRC patients can obtain more benefits, and this once again determined the value of aspirin in primary prevention of CRC. A prospective study showed that among the registered 130,251 healthy subjects, after a 32-year follow-up survey, 27,985 people had cancer (20,414 women). Those who regularly take aspirin (0.5–1.5 standard aspirin tablets/week, 163 mg to 488 mg) for at least 6 years would reduce the overall risk of cancer by 3%, gastrointestinal cancer incidences reduce, including CRC (19% lower risk) and gastroesophageal cancer, but the risks of non-gastrointestinal cancer (such as breast cancer, advanced prostate cancer, lung cancer, etc.) were not significantly reduced. Importantly, retrospective epidemiological studies have shown that low-dose aspirin (75 mg/day) is more effective in reducing morbidity
and mortality associated with CRC than high-dose aspirin (325–1200 mg/day).8

In April 2016, the USPSTF19 reviewed a number of large randomized controlled trials (RCTs) in the use of aspirin to prevent cancer, and found that taking aspirin for 3.6–10.1 years showed no significant difference in the overall cancer mortality and incidence between the aspirin group and the normal control group. The 20-year mortality rate of CRC was significantly lower in the aspirin group (four RCTs, RR=0.67), and the incidence of CRC was reduced for those taking aspirin for 10–19 years (three RCTs, total number of cases 47464, relative risk [RR]=0.60). In view of this, the USPSTF eventually issued aspirin as a guide for cardiovascular disease (CVD) and primary prevention of CRC, and ultimately recommended that: adults aged 50–69 years, 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin (75 mg/daily) for at least 10 years, should consider taking low-dose aspirin to prevent CVD and CRC. The working group here considered the benefits of the various protocols that have been demonstrated in primary prevention trials, including doses of 75 and 100 mg per day and doses of 100 and 325 mg aspirin every day. The daily dose of 75 mg seems to be as effective as the higher dose (325 mg). However, the risk of gastrointestinal bleeding may increase with the increased doses. Comprehensive consideration is given that aspirin should be taken at 50–325 mg/day. Meanwhile, the guidelines also emphasize the need for trade-offs and individualization of aspirin-induced bleeding and other risks and benefits. It is worth mentioning that in the USA, the most commonly prescribed dose is 81 mg per day. In addition, we have summarized the main recommendations of the USPSTF in Table 1.

**Antitumor mechanism of non-steroidal anti-inflammatory drugs (NSAIDs)**

**Inhibition of COX-2**

Most of the NSAIDs are thought to act as tumor suppressors by inhibiting cyclooxygenase-COX.20 COX is known

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**Table 1** Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer in the USA: clinical summary19

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Recommended instructions</th>
<th>Treatment and dosage</th>
<th>Balance of benefits and harms</th>
<th>Risk assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults younger than 50 years</td>
<td>No recommendation. grade I</td>
<td>The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years</td>
<td>A reasonable approach consistent with the evidence is to prescribe 81 mg/d (the most commonly prescribed dose in the USA), and assess CVD and bleeding risk factors starting at age 50 y and periodically thereafter, as well as when CVD and bleeding risk factors are first detected or change.</td>
<td>The benefits of aspirin use outweigh the increased risk for bleeding by a moderate amount.</td>
<td>Primary risk factors for CVD are older age, male sex, race/ethnicity, abnormal lipid levels, high blood pressure, diabetes, and smoking. Risk factors for GI bleeding with aspirin use include higher aspirin dose and longer duration of use, history of GI ulcers or upper GI pain, bleeding disorders, renal failure, severe liver disease, and thrombocytopenia.</td>
</tr>
<tr>
<td>Adults aged 50–59 years with ≥10% CVD risk</td>
<td>Initiate low-dose aspirin use. Grade B</td>
<td>Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years</td>
<td>The benefits of aspirin use outweigh the increased risk for bleeding by a small amount.</td>
<td>The evidence on aspirin use is insufficient and the balance of benefits and harms cannot be determined.</td>
<td></td>
</tr>
<tr>
<td>Adults aged 60–69 years with a ≥10% CVD risk</td>
<td>The decision to initiate low-aspirin use is an individual one. Grade C</td>
<td>Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin. (C recommendation)</td>
<td>The evidence on aspirin use is insufficient and the balance of benefits and harms cannot be determined.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults aged 70 years or older</td>
<td>No recommendation. grade I</td>
<td>The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CVD, cardiovascular disease; CRC, colorectal cancer; GI, gastrointestinal.
to convert arachidonic acid to prostaglandins (PGs), and
the PGs overexpression are thought to be early events in
a variety of oncogenic events. COX has three structural
subtypes, structural COX-1 and inducible COX-2 (selectiv-
ity), COX-3 (found in the nervous system appears late in
the inflammatory response). COX-1 is mainly present
in normal tissue cells and catalyzes the production of PGs
that maintain normal physiological function. COX-2 is a
membrane-bound protein. In normal physiological status,
the majority of tissue cells do not express COX-2; but in
inflammation, tumor and other pathological conditions, due
to inflammatory substances and carcinogenic substances
such as the inflammatory mediators induced, COX-2 shows
an increasing expression, and participates in a variety of
pathophysiological processes, causing canceration (large
number of COX-2-dependent genes are involved in this
tumorigenesis process). Krysan et al found that COX-2
is usually upregulated in carcinoma in situ and non-small-
cell lung cancer. Chen et al showed that the high expression
of COX-2 in tumor tissue upregulated the expression of
bcl-2 and thus played the role of an antiapoptotic effect of
tumor cells. In addition, COX-2 and PG overexpression in
chronic inflammation suggest that PGs produced by COX-2
catalysis can induce neovascularization to a certain extent
and provide nutrition for tumor survival and proliferation.
Finally, the COX-2 can affect upregulation of matrix metal-
loproteinase-2 expression which then promotes tumor
invasion and metastasis. Recent studies have shown that
the specific COX-2 enzyme inhibitor celecoxib (a NSAID)
can effectively inhibit various tumor cell proliferation and
provide apoptosis on Raji cells, SK-N-SH cells and
K562 cells in vitro. In addition, Harris et al conducted a
case–control study of NSAID in 489 lung cancer patients
and 978 control subjects. The results showed that a daily
intake of aspirin or ibuprofen for at least 2 years reduces the
relative risk of lung cancer by 68% ($P < 0.01$). The detection
of COX-2 in patients also suggested that patients taking
NSAIDs such as naproxen used on culture bladder cancer cells
can locate the apoptotic protein precursor Apaf-1 to the mito-
chondrial membrane so that it cannot play a role in apoptosis.
Yang et al and Xu et al used aspirin to treat human
small cell lung cancer A549 cells, ovarian cancer SK-OV-3
cells and showed the expression of bcl-2 gene decreased and
the expression of bax gene increased. Kim found that strong
NSAIDs such as naproxen used on culture bladder cancer cells
causenificant cell apoptosis, which was mainly due to the
downregulation of bcl-2 gene and the upregulation of bax
gene. In addition, Bank et al found that NSAIDs sulindac
acid can degrade antiapoptotic protein bcl-XL, block bcl-XL
antagonism of bax, make pro-apoptotic protein bax activation
cascade reaction, then activate the cell apoptosis pro-
ger. Raza et al found that amino salicylic acid can increase
the production of intracellular ROS, reduce intracellular glu-
thione storage, and inhibit mitochondrial respiratory chain
enzyme complex, electron transport chain complex Body I,
electron transport chain complex IV, mitochondrial matrix
enzyme, cis-aconitase and other enzyme activity. The mito-
chondrial permeability changes can then lead to the synthesis
of ATP being blocked, bcl-2 expression downregulated, and
the release of cytochrome C will eventually trigger apoptosis.
Furthermore, celecoxib can increase the wild-type p53 gene
cancer overexpressing the p53 protein. The upregulation of
p53 protein expression could further upregulate the expression
of p53up-regulated modulator of apoptosis (PUMA) protein,
which is the p53 gene downstream positive regulator. PUMA
encodes the BH3-only protein of the bcl-2 family, whereas the
BH3-only protein is a key factor in the initiation of apoptosis
by the p53 pathway.

**Downregulation of EGFR expression**

Recently, Dong et al found that in 80% of patients with
colorectal cancer EGFR overexpression occurred, but it can
be downregulated by regular use of aspirin. Similarly, they
noted that EGFR and COX-2 were co-located in patients with
familial multiple adenomas and that COX-2 overexpression
triggers proto-oncogene c-Jun-dependent transcription fac-
tors which bind to the EGFR promoter activation of protein-1
and can further promote the accumulation of EGFR cells in
cells and promote their transformation to malignant.

**Protect and repair DNA damage**

Oxidative stress plays an important role in the development of
various diseases such as cancer, cardiovascular disease, etc
and can damage nucleic acid, protein, membrane and other
cell elements. Banti et al mentioned that aspirin counteracts
exogenous bacterial infections by inhibiting the production of peroxides, and oxygen radicals produced by bacteria, and can therefore cause great damage to cellular DNA. Chen et al. confirmed that aspirin can inhibit the formation of nucleic acid cleavage and hydroxyl radicals caused by peroxynitrite, which play a role in protecting DNA. Goel et al. found that aspirin could induce high expression of DNA mismatch repair proteins hMLH1, hMSH2, hMSH6 and hPMS2 in colon cancer cells, and the high expression of hMLH1 and hMSH2 could induce tumor cell apoptosis. Dibra et al. found that aspirin can induce X-ray repair of cross-complementary gene 3 (XRCC3) and its protein expression, thus promoting DNA self-healing.

The general antitumor mechanism of NSAIDs is summarized in Table 2.

The new thinking on the apparent phenomenon
Individual differences bring non-universality
A recent study in 2012 set out aspirin as a research boom in CRC secondary prevention. Liao et al. retrospectively analyzed 964 patients with CRC and found that CRC-related mortality was significantly reduced (RR=0.18) and the overall survival extended (RR =0.54) in patients with CRC who had been diagnosed with aspirin-treated PIK3CA mutations. In contrast, in PIK3CA wild-type patients, regular aspirin administration (twice a week or more, standard dose of 325 mg aspirin tablets) after diagnosis did not improve CRC patients specific survival (RR=0.96) or overall survival (RR=0.94). In addition, some studies have shown that patients with 15-PGDH (15-hydroxyprogesterone dehydrogenase) and antigen-specific HLA-1 high expression in colon cancer can achieve more benefits in aspirin therapy (twice a week or more, standard dose of 325 mg aspirin tablets). Based on this, whether PIK3CA, 15-PGDH and HLA-1 can be used as key molecular biomarkers in the treatment of CRC is worthy of consideration.

NSAIDs prevents cancer from escaping immune surveillance
In 2015, Zelenay et al. demonstrated that skin cancer, breast cancer and CRC cells often produce large amounts of PGE2, which can attenuate the immune system’s normal response to diseased cells and help cancer cells to hide. This process allows the tumor to grow rapidly, and therefore explains why some immunotherapy has difficulty in achieving the desired effect. Aspirin is a kind of COX inhibitor, which can inhibit the synthesis of PGE2 to achieve the effect of re-awakening the immune system. Therefore, compared with the use of immunotherapy alone, the combination of immunotherapy with aspirin or other COX inhibitors can significantly reduce the growth of CRC or melanoma in mice. In addition, a study showed that platelets can also help tumor cells escape the immune system. In vivo platelet-specific Glycoprotein A Repetitions Predominant (GARP) can activate platelet-derived or non-platelet-derived TGFβ, and GARP-TGFβ complex can effectively reduce the activity of T-cell activity at the physiological level. Thus most tumor cells can escape the clearance of the immune system, and the use of platelet antagonists will significantly improve the killing of tumor cells by the immune system. Therefore, the administration of COX inhibitor or platelet antagonists simultaneously with the patient’s immunotherapy can make cancer immunotherapy more effective and may become a new treatment with great potential.

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Target</th>
<th>Pathway</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Downregulate COX-2 expression</td>
<td>Downregulation of bcl-2 expression</td>
<td>Cell apoptosis</td>
</tr>
<tr>
<td>Aspirin/naproxen</td>
<td>Downregulation of bcl-2 expression and up-regulation of bax expression</td>
<td>Downregulation of mmp-2 expression, Caspase cascade reaction</td>
<td>Reduce tumor cell invasion</td>
</tr>
<tr>
<td>Sulindac acid</td>
<td>Degrade antiapoptotic protein bcl-XL</td>
<td>Pro-apoptotic protein bax activation caspase cascade reaction</td>
<td>Cell apoptosis</td>
</tr>
<tr>
<td>Amino salicylic acid</td>
<td>Increase reactive oxygen species</td>
<td>The mitochondrial permeability changes; bcl-2 expression down regulated</td>
<td>Cell apoptosis</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Increase p53 gene expression</td>
<td>Uregulation of PUMA and BH3-only expression</td>
<td>Cell apoptosis by the p53 pathway</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Upregulation of hMLH1, hMSH2, hMSH6 and hPMS2 expression</td>
<td>Upregulation of XRCC3 expression</td>
<td>Promote DNA self-healing</td>
</tr>
</tbody>
</table>

**Abbreviations:** COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs; XRCC3, X-ray repair of cross-complementary gene 3.
Aspirin, platelet, tumor

Recent reports show that patients with a high blood platelet count are significantly more likely to develop cancer than those with a low blood platelet count, suggesting that tumor development may be associated with platelets.\(^{50}\) It is known that platelets, in addition to coagulation, play a role in the formation of new blood vessels.\(^{51}\) This effect is usually beneficial, such as the formation of a new clot after injury, and the need for new blood vessels to regulate blood flow. However, the same effect will also help the tumor growth. Platelets can enhance the invasiveness of cancer cells,\(^{48}\) promote epithelial-mesenchymal transition (EMT) transformation,\(^{52}\) and contribute to the deterioration of cancer to a large extent. In addition, cancer as a long-term chronic injury process will inevitably produce various mechanical damage etc. and promote the self-aggregation of platelets in the cancer site. There is already evidence that platelets can be spontaneously recruited to colon cancer cells in patients with colon cancer,\(^{53}\) which will undoubtedly greatly increase the progression of cancer. So we speculate that use of platelet antagonists can effectively slow down the progression of cancer. Lichtenberger et al\(^{54}\) indicated that aspirin can inhibit the activity of COX-1 enzyme, control the number of circulating platelets and their activity levels, and therefore block the interaction between platelets and cancer cells. They used platelet co-culture of human and murine colon cancer cell layers with two different aspirin preparations (normal aspirin and combination of phosphatidylcholine-specific aspirin) and found that platelets can significantly promote tumor cell proliferation and enhance its ability to migrate, while the use of aspirin can significantly decline the effect, and the effect of special aspirin (aspirin and phosphatidylcholine mixture) had increased efficacy. Other previous studies\(^{55}\) used platelets as a carrier to deliver PD-L1 antibody to the tumor site to achieve targeted killing of tumor cells and suggested that the role of platelets in the development of tumors is not absolute. Therefore, changing the traditional thoughts on cancer treatment would make us gain more benefits in the fight against tumors.

Aspirin against cancer by slowing up the mutation accumulates

It is known that tumorigenesis is caused by long-term accumulation of genetic mutations. Kostadinov et al\(^{56}\) suggested that aspirin can prevent cancer by slowing the accumulation of DNA mutations in abnormal cells in precancerous lesions. They analyzed 13 biopsy samples from patients with Barrett’s esophagus and conducted a 6–19 years follow-up studies. In the “observational crossover” studied, some patients began taking aspirin daily initially for several years and then stopped taking it, while others took aspirin until the end of the observation. The biopsy results showed that patients who did not use aspirin showed more than 10 times faster accumulations of gene mutations than those who used aspirin long term.

Different forms of NSAIDs may have different effects

In addition to traditional formulations of NSAIDs for the prevention and treatment of tumor, various forms of NSAIDs become available for tumor prevention or treatment either in vivo or in vitro. One example is the use of aspirin-phosphatidylcholine in vitro achieved better results in human or murine colon cancer cell lines at the cellular level compared to traditional aspirin.\(^{53}\) In addition, another study\(^{57}\) showed that the use of nano-forms of aspirin and ibuprofen to treat lung cancer patient’s whole blood in vitro could effectively reduce the DNA damage of white blood cells, which suggested that the nano-form of NSAIDs is more likely to enter the cell membrane and bind to DNA. It is worth mentioning that the use of metal complexes could also enhance the affinity of the complex for DNA binding.\(^{42}\) Therefore, NSAIDs and metal complexes should be taken into consideration in the treatment of cancer. Compared with traditional NSAIDs, NSAIDs with bio-metals show better pharmacological activity,\(^{58}\) and lower gastrointestinal toxicity.\(^{59}\) In addition, different metal and NSAIDs complexes are selective for different cell lines, for example, the platinum complexes of the NSAIDs tomedine and indomethacin have the higher selectivity on non-cancerous cells BHK21 and L929.\(^{42}\) This suggests that we can choose different metal complexes as ligands to modify NSAIDs and to achieve selective killing of tumor cells.

In addition, as early as 2013, Liu et al\(^{60}\) conducted a meta-analysis of 10 studies between 2003 and 2013 and concluded that the use of aspirin and other NSAIDs did not significantly affect the incidence of brain tumors and was not associated with special subtypes of brain tumor. However, Simms et al\(^{61}\) showed that in vivo the liquid containing aspirin may be able to extend the life of thousands of patients with brain cancer. This is a breakthrough result in which they found that liquid aspirin can pass through the blood–brain barrier (known in the treatment of brain tumor, the blood–brain barrier can prevent chemotherapy drugs passing into the brain to kill brain tumor cells), and early tests showed that compared to existing chemotherapy drugs, liquid aspirin can kill brain
cancer cells to improve the efficiency ten-fold. Therefore, we speculate that the role of aspirin in tumor treatment may be associated with the use of drug forms.

Enhance the effect of antitumor therapy
Some NSAIDs can enhance the sensitivity of the tumor to chemotherapy drugs, thus antitumor drugs and NSAIDs combination can produce a better prognosis in tumor therapy. Huang et al found that for in vitro culture of glioma cells, the combination can produce a better prognosis in tumor therapy. Indomethacin has been demonstrated to downregulate the expression of ABCG2, MDR1 and MRP1, which were colloidal tumor-associated resistance genes, so that the antitumor effect of chemotherapeutic drugs was significantly improved. In addition, indomethacin does not only downregulate the resistance genes, but also enhances the sensitivity of colon cancer cells to chemotherapy drugs. 5-fluorouracil (5Fu) is known as a common cancer chemotherapy drug. Réti et al found that in patient body 80% 5Fu could metabolize into 5, 6-dihydro-5-fluorouracil by dihydropyrimidine dehydrogenase and lost the activity. And taking indomethacin could increase the concentration of 5Fu in vivo by inhibiting the activity of dihydropyrimidine dehydrogenase; thereby the increasing concentration of 5Fu can enhance the toxicity to tumor cells. Cheng et al demonstrated a new technique by using nucleophilic substitution to combine tumor chemotherapeutic drug cisplatin and aspirin which can significantly reduce the drug resistance of cisplatin in tumor therapy. Finally, in a recent study, the researchers found that when using combination of aspirin and clopidogrel (antiplatelet drugs) to treat melanoma-bearing mice, the mice obtained longer survival and fewer relapses when receiving adoptive T-cell therapy, suggesting that antiplatelet drugs could attenuate the ability of platelets to help tumor cells escape immune clearance. It is fair to say that the combination of NSAIDs and traditional cancer therapies or adoptive T cell therapy therefore could lead to a further breakthrough in cancer therapy with “1+1>2.”

All the above new thoughts are summarized in Table 3.

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Target</th>
<th>Target function</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>PGE2</td>
<td>Attenuate the immune system’s normal response to diseased cells and help cancer cells to hide</td>
<td>Inhibit the synthesis of PGE2</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Platelets</td>
<td>In vivo platelet-derived or non-platelet-derived TGFβ and GARP complex can effectively reduce the activity of T-cell activity Platelets spontaneously recruited help the tumor growth, enhance the invasiveness, promote EMT transformation</td>
<td>Inhibit the activity of COX-1 enzyme, control the number of circulating platelets and their activity levels</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Genetic mutations</td>
<td>Tumorigenesis is caused by long-term accumulation of genetic mutations</td>
<td>Slow down gene mutation accumulation and protect normal cell DNA</td>
</tr>
<tr>
<td>Aspirin</td>
<td>DNA damage</td>
<td>Gene damage increases the chance of DNA sequence changes</td>
<td></td>
</tr>
<tr>
<td>Aspirin/Indomethacin</td>
<td>Traditional chemotherapy drugs therapy</td>
<td>Direct killing of tumor cells by multiple ways</td>
<td>Increase drug toxicity and downregulate cellular drug resistance</td>
</tr>
<tr>
<td></td>
<td>Adoptive T-cell therapy</td>
<td>Organism’s own T cells are propagated in vitro and chosen specifically to recognize tumor cells. The culture is expanded and then returned to the cancer patients</td>
<td>Attenuate the ability of platelets to help tumor cells escape immune clearance</td>
</tr>
</tbody>
</table>

Table 3 The new thinking about NSAIDs inhibiting tumors

Abbreviations: GARP, Glycoprotein A Repetitions Predominant; NSAIDs, nonsteroidal anti-inflammatory drugs; PGE2, prostaglandin E2.
reasonable choice of population and dose, to achieve the largest anticancer benefits. As the body’s own platelets are linked to tumor growth and metastasis during tumorigenesis, our in vitro study found that platelets promote the proliferation of tumor cells and this effect can be inhibited by aspirin (unpublished data). In addition, a prospective cohort study showed that thrombocytosis is positively associated with tumor incidence. Of all the 9,435 male thrombocytocytia patients, 1,098 were diagnosed with cancer (11.6%; 95% CI = 11.0–12.3), however, only 106 out of 2,599 men without thrombocytosis had cancer (4.1%; 95% CI = 3.4–4.9). Similarly, a total of 1,355 out of 21,826 females with thrombocytosis developed cancer (6.2%; 95% CI = 5.9–6.5), compared with 119 of 5,370 females without (2.2%; 95% CI = 1.8–2.6). Our previous in vivo studies also showed that the effect of platelets on adenoma cells is two-sided, but this effect can be attenuated by the platelet antagonist aspirin (unpublished data). Furthermore, our in vivo experiments have shown that aspirin has a certain effect on inhibiting tumor metastasis and both the duration and varying time periods of drug use could affect the survival of tumor-bearing mice (unpublished data). Further research work should focus on exploring the relationship between platelet, cancer and aspirin, clarifying the role of platelets in tumorigenesis and development, evaluating which stage of aspirin intervention could gain more benefits, proposing potential molecular mechanisms and new ideas for aspirin in clinical cancer prevention and treatment.

Disclosure
The authors report no conflicts of interest in this work.

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