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REVIEW – CANCER RESEARCH

Beyond a chemopreventive reagent, aspirin is a master regulator of the hallmarks of cancer

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Abstract

Purpose Aspirin, one of the most commonly used nonsteroidal anti-inflammatory drugs (NAIDS), not only shows cancer chemoprevention effects but also improves cancer therapeutic effects when combined with other therapies. Studies that focus on aspirin regulation of the hallmarks of cancer and the associated molecular mechanisms facilitate a more thorough understanding of aspirin in mediating chemoprevention and may supply additional information for the development of novel cancer therapeutic agents.

Methods The relevant literatures from PubMed have been reviewed in this article.

Results Current studies have revealed that aspirin regulates almost all the hallmarks of cancer. Within tumor tissue, aspirin suppresses the bioactivities of cancer cells themselves and deteriorates the tumor microenvironment that supports cancer progression. In addition to tumor tissues, blocking of platelet activation also contributes to the ability of aspirin to inhibit cancer progression. In terms of the molecular mechanism, aspirin targets oncogenes and cancer-related signaling pathways and activates certain tumor suppressors.

Conclusion Beyond a chemopreventive agent, aspirin is a master regulator of the hallmarks of cancer.

Keywords Aspirin · Cancer · Hallmark of cancers · Cancer therapy

Background: aspirin and cancer chemoprevention

Acetylsalicylic acid, also known as aspirin, was first synthesized in 1897. As one of the most frequently used nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin acts as an antipyretic, analgesic and anti-platelet agent in clinical use (Collaborative overview of randomised trials of anti-platelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged anti-platelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration 1994; Ekinci et al. 2011; Mitchell and Broadhead 1967; Rowland et al. 1967) and has currently attracted substantial interest in the cancer chemoprevention of various cancer types. The anti-cancer effect of aspirin was first reported in a colorectal cancer animal model in the 1970s (Gasic et al. 1972). Large

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quantities of randomized clinical trials were conducted in order to explore the cardiovascular protective effect of aspirin in the 1980s (Capodanno and Angiolillo 2016). And thus, these trials accidentally provided an insight into the association between aspirin and cancer risk (Cao et al. 2016b). Before the end of the twentieth century, researches on aspirin in cancer prevention and treatment were burgeoning. Several observational studies suggested no benefit from aspirin in the prevention of colorectal adenoma or colorectal cancer (Kim et al. 2018; Okada et al. 2018; Paganini-Hill et al. 1989, 1991, 1992), and recently, a large-scale clinical trial conducted by McNeil JJ et al. indicates that aspirin use has no apparent beneficial effects on healthy elderly persons (McNeil et al. 2018c), and even brings them higher all-cause mortality (McNeil et al. 2018a) and higher risk of major hemorrhage (McNeil et al. 2018b). However, most research has shown that aspirin inhibits carcinogenesis and the progression of various cancer types (Cuzick et al. 2009; Hua et al. 2018a; Zhang et al. 2016a). Recently, the cancer chemopreventive effect of aspirin has been well-recognized based on numerous large-scale epidemiological studies, in which cumulative evidence demonstrates that regular use of aspirin not only significantly reduces the incidence of colorectal cancer, but also reduces the metastasis and mortality of this disease (Algra and Rothwell 2012; Flossmann and Rothwell 2007; Rothwell et al. 2012). Additionally, it has been demonstrated that aspirin combined with other therapeutics improves the cancer therapeutic effect. For instance, aspirin treatment in combination with chemotherapy is correlated with improved survival and lower recurrence of colorectal cancer (CRC) (Ng et al. 2015), and its combination with immune-checkpoint blockade produces strong anti-cancer immunity (Zelenay et al. 2015). Currently, a phase III, double-blind, placebo controlled, randomized trial (ADD-ASPIRIN) has been performed in 2016 to investigate whether regular use of aspirin after standard therapy has the potential to prolong the survival and prevent recurrence in patients with non-metastatic solid tumors (including colorectal, breast, prostate and gastro-esophageal cancer) (Coyle et al. 2016).

These results from clinical trials and epidemiological studies triggered extensive interest in investigating the underlying mechanisms of the anti-cancer effects of aspirin. Some reviews have already summarized the researches about aspirin in cancer prevention and treatment and discussed the putative molecular targets regulated by aspirin (Cao et al. 2016a; Cuzick et al. 2009; Hua et al. 2018b; Patrignani and Patrono 2016; Thun et al. 2012). However, how aspirin regulating the hallmarks of cancer is not elaborated intensively. Moreover, numerous new findings about aspirin regulating cancer immunity and immunotherapy require to be highlighted timely. Additionally, combination of the target molecules of aspirin with the molecular mechanisms regulating cancer hallmarks would make the anti-cancer mechanisms of aspirin more integrative and impressive. Therefore, in this review, we elaborate the current knowledge related to aspirin regulating the hallmarks of cancer and the associated potential molecular mechanisms.

Effects of aspirin on the hallmarks of cancer and related mechanisms

During cancer development, cancer cells acquire certain special capabilities that differ from those of normal cells to promote cancer progression. These biological capabilities of cancer cells, also known as the hallmarks of cancer, include persistent proliferation, loss of suppressor signaling, acquisition of sustained growth signal, immortality, invasion and metastasis, angiogenesis, resistance to cell death, genome instability, evasion of anti-cancer immunity, metabolism shifts and induction of cancer-associated inflammation (Hanahan and Weinberg 2011). Studies have demonstrated that aspirin regulates almost all of these hallmarks of cancer (Fig. 1).

Aspirin reverses the reprogramming of energy metabolism in cancer cells

Compared with normal cells, cancer cells exclusively prefer glycolysis over mitochondrial oxidative phosphorylation, even under aerobic conditions. This phenomenon is known as the Warburg effect or aerobic glycolysis (Koppenol et al. 2011). Current studies showed that aspirin is able to suppress the reprogramming of energy metabolism in cancer cells.

The mechanistic target of rapamycin (mTOR) is a key kinase complex involved in the survival, proliferation and metastasis of cancer cells. The mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) are two distinct sub-types of mTOR. mTORC1 primarily regulates protein, lipid and nucleotide synthesis and metabolism, which are essential to cell growth (Saxton and Sabatini 2017). It has been demonstrated in cancer cells that mTOR1 contributes to a shift in glucose metabolism from oxidative phosphorylation to glycolysis. Different from mTORC1, mTORC2 primarily regulates the proliferation, metastasis and survival of cancer cells via phosphorylation of the AGC (PKA/PKG/PKC) family of protein kinases (Saxton and Sabatini 2017). The activity of mTORC1 can be regulated by adenosine 5′-monophosphate activated protein kinase (AMPK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB/AKT) signaling. AMPK, as a hub of various metabolic crosstalk, plays an especially crucial role in regulating energy homeostasis and protecting cells from stress. AMPK is a heterodimer of the α, β,

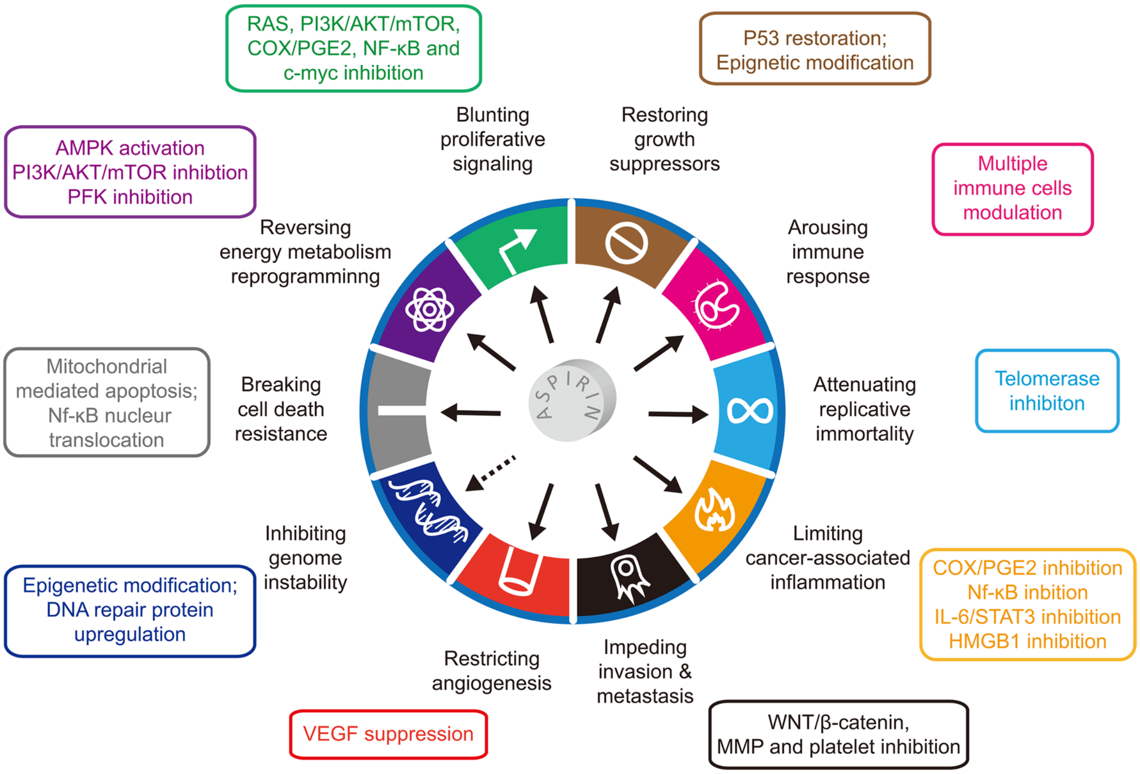

Fig. 1 Aspirin regulates ten hallmarks of cancer

and γ subunits and acts as a critical energy sensor by monitoring the cellular adenosine 5′-monophosphate (AMP)/adenosine 5′-triphosphate (ATP) ratio (Hardie 2008). When cells face hypoxia, ischemia or starvation, the cellular ATP level is remarkably decreased, accompanied by AMP accumulation. Excessive AMP competitively binds to the γ subunit of AMPK and activates this kinase. Many other stimuli can activate the AMPK pathway, including hormones, stress, and drugs (Hardie 2008). Salicylate, the metabolite of aspirin, is found to directly activate AMPK in HEK-293 cells (Hawley et al. 2012). The activation of AMPK mediated by salicylate is not associated with the change of cellular level of AMP, but causes the allosteric activation of the kinase and inhibits dephosphorylation of activating phosphorylation site (Thr172) by protein phosphatase (Hawley et al. 2012). Additionally, aspirin contributes to AMPK activation and mTORC1 inhibition in PIK3CA-mutant breast cancer cells (Henry et al. 2017), suggesting aspirin targets AMPK/mTOR signaling and presumably inhibits energy metabolism in these cancer cells. Nevertheless, the activation of AMPK induced by aspirin (5 mM) was also found to promote mTORC2, which boosts pro-survival protein myeloid cell leukemia 1 (MCL-1) expression via the AMPK-mTORC2-Akt/extracellular signal-regulated kinase (ERK) axis in HepG2 cells and SW480 cells (Gao et al. 2016). MCL-1 is regarded as a canonical anti-apoptotic protein that is commonly overexpressed in various cancers (Kotschy et al. 2016). Thus, the AMPK activation induced by aspirin not only activates mTORC1 but also elevates mTORC2 and its target MCL-1, and the latter effect might compromise the anti-cancer effect of aspirin to a certain degree. Therefore, aspirin combined with other reagents, such as MCL-1 inhibitors, might achieve a more effective anti-cancer effect. Additionally, PI3K/AKT signaling, located upstream of mTOR, is activated in most cancer types, and the overexpression of cyclooxygenase (COX) is one of the reasons for the activation of this signaling in several cancer types (Majumder et al. 2016; Uddin et al. 2010). As a well-known COX inhibitor, aspirin is also proved to restrain the activity of PI3K/AKT signaling both in MDAH2774 and SKOV3 cell lines and in epithelial ovarian cancer animal model (Uddin et al. 2010) and might possibly suppress mTOR activation.

In addition to targeting AMPK and PI3K/AKT-regulated mTOR, 6-phosphofructo-1-kinase (PFK) is a recently identified novel target of aspirin. PFK is a key enzyme that regulates the irreversible step of glycolysis. Aspirin and salicylic acid have been reported to modulate PFK structure and inhibit its activity in a dose-dependent manner in breast cancer cell line MCF-7, thus reversing the metabolism shift in cancer cells (Spitz et al. 2009).

Aspirin limits cancer-associated inflammation

It is well established that inflammation stimulates multiple cytokine secretions and various types of cell infiltration, which supply a suitable environment for cancer development and progression (DeNardo et al. 2010; Grivennikov et al. 2010; Karnoub and Weinberg 2006; Qian and Pollard 2010). As an NSAID, aspirin is a potent anti-inflammation reagent and thus limits cancer progression.

Cyclooxygenase-2 (COX-2) is a potent inflammation regulator that catalyzes the synthesis of the prostaglandin H2 (PGH2) using arachidonic acid as a substrate, which is converted to prostaglandin E2 (PGE2) with catalysis of prostaglandin E synthetase (PGES) (Phillips et al. 2014). PGE2 is a pivotal pro-inflammatory factor, which contributes to multiple hallmark capabilities that participate in the tumorigenesis of many cancer types by the activation of various cellular signaling pathways and is closely related to carcinogenesis and cancer progression (Markowitz 2007; Nakanishi and Rosenberg 2013). John R. Vane demonstrated that aspirin irreversibly acetylates COX and blocks the generation of PGE2, and this breakthrough finding earned John R. Vane the Nobel Prize in 1982 (Vane 1971). Because COX is the target of aspirin and plays critical roles in carcinogenesis and cancer progression, the inhibition of COX activity is one of the most important mechanisms that explain the anti-cancer properties of aspirin (Dovizio et al. 2012; Thun et al. 2012).

Transcription factor nuclear factor-κB (NF-κB) is an important molecule that simultaneously participates in inflammation and carcinogenesis. The NF-κB family consists of Rel-A (p65), Rel-B, c-Rel, p105/p50 and p100/p52 in mammalian cells. When these family members bind with the inhibitor of κB (IκB) in the cytoplasm, NF-κB maintains a silent form. Once activated by its upstream signaling, the IκB kinases composed of IKK-α, β and γ (NEMO) can phosphorylate IκB. The phosphorylation of IκB causes degradation itself and releases NF-κB, and free NF-κB translocates from the cytoplasm to the nucleus and activates the transcription of inflammatory factors. It has been historically well-recognized that aspirin inhibits the activation of NF-κB. The literature suggests two models for aspirin inhibition of the NF-κB signaling pathway, and both models are associated with IκB. In most conditions, aspirin and sodium salicylate inhibit the degradation of IκB through IKK-β binding at millimolar concentration (Yin et al. 1998) and thus block the translocation of NF-κB from the cytoplasm to the nucleus at the early stage after treatment (Chen and Stark 2017; Kopp and Ghosh 1994; Liao et al. 2015), whereas prolonged treatment with 500 μM of aspirin increases the phosphorylation and degradation of IκB and thus facilitates the nuclear translocation of NF-κB (Chen and Stark 2017; Din et al. 2004; Stark et al. 2001). Although aspirin stimulates NF-κB entry into the nucleus, the transcriptional activity of NF-κB is usually suppressed due to NF-κB segregation in the nucleolus through interaction with nucleolar proteins, such as NFBP and $p14^{ARF}$ (Chen and Stark 2017; Dhar et al. 2004; Rocha et al. 2003; Stark and Dunlop 2005; Sweet et al. 2003).

Additionally, interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) is also an important signal that mediates inflammation and carcinogenesis (Yue et al. 2014). The pro-inflammatory IL-6 stimulates the activation of STAT3 in an autocrine manner (Fukuda et al. 2011). And the activation of STAT3 directly regulates the transcription of genes related to proliferation, survival, migration, angiogenesis and anti-tumor immune suppression in cancer cells (Gao et al. 2017b) and thus correlates with poor prognosis in human cancers (Horiguchi et al. 2002; Kawada et al. 2006; Masuda et al. 2002; Morikawa et al. 2011). It has been demonstrated that daily 500 μg of aspirin inhibits the activation of STAT3 signaling and suppresses the growth of CRC cells in inflammation-related CRC animal models (Tian et al. 2011).

High-mobility group box 1 (HMGB1) is also a key inflammatory molecule that contributes to carcinogenesis and the progression of certain neoplasms (Choi et al. 2003; Flohr et al. 2001; Meyer et al. 2004; Tang et al. 2010). HMGB1 not only mediates the release of tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and other inflammatory products but also participates in cell infiltration (Tang et al. 2010). These important functions induced by HMGB1 may lead to chronic inflammatory responses in the context in which cancer develops (Dong Xda et al. 2007) and chronic inflammation can in return enhance cancer development (de Visser and Coussens 2006). Additionally, the overexpression of HMGB1 is related to multiple hallmarks of cancer, such as evasion of apoptosis, angiogenesis and metastasis (Tang et al. 2010). Aspirin (25 or 50 mg/kg/day) have been reported to suppress the growth of mesothelioma in mice model via the inhibition of HMGB1-mediated tumor progression (Yang et al. 2015).

Aspirin arouses immune responses to eliminate cancer cells

Tumor cells often escape from the immune surveillance and elimination by host immune system via multi-mechanisms (Chen and Mellman 2013). In 2013, Daniel et al. has reviewed the cancer-immunity cycle which mainly consists of seven steps, including release of cancer cell antigens, cancer antigen presentation, priming and activation, trafficking of T cells to tumors, infiltration of T cells into tumors, recognition of cancer cells by T cells and killing of cancer cells (Chen and Mellman 2013). Recent studies have suggested that aspirin affects most of these steps in cancer-immunity cycle and beneficially arouses immune responses to eliminate cancer cells.

Aspirin is capable to improve the efficacy for chemotherapy in cancer treatment. It is reported that aspirin potentiates the anti-tumor effects of cisplatin (Kumar and Singh 2012). An observational study also demonstrated that aspirin use during chemotherapy is associated with improved outcomes of stage Ш colon cancer patients (Ng et al. 2015). Besides, a recent research also found that doxorubicin (0.5 µM), combing with low-dose aspirin (~200 mg/ml), would bring a greater killing efficacy on MDA-MB-231 cancer cell than doxorubicin use alone (Khoo et al. 2019). Apart form chemotherapy, studies also uncovered aspirin's potential action as an adjuvant in radiotherapy. For instance, an observational study found that aspirin is associated with reduced mortality of men treated with chemotherapy for prostate cancer (Choe et al. 2012). All these studies suggested that aspirin facilitates chemotherapy and radiotherapy to kill cancer cells which mediates the release of cancer cell antigens. Besides, aspirin (20 mg/kg wt) combined with cisplatin (50 mg/kg wt I.P.) restricts the secretion of IL-4 and IL-10 in mouse models of Dalton's lymphoma, the cytokines inhibiting cancer antigen presentation (Kumar and Singh 2012). COX-catalyzed production of PGE2 undermines the natural killer cell mediated conventional type 1 dendritic cells (cDC1) recruitment (Bottcher et al. 2018), thus impedes cancer antigen presentation. Accordingly, COX-inhibition blocking the release of tumor derived-PGE2 is helpful to revive cDC1 recruitment and facilitates cancer antigen presentation. Aspirin also inhibits synthesis and secretion of prostaglandins which suppresses T lymphocyte priming and activation (Chen and Mellman 2013). Apart of prostaglandins, PD-1 and its ligand PD-L1 are also barricades for T cell priming and activation (Chen and Mellman 2013). Notably, 600 mg/ml aspirin in drinking water administration synergizes with anti-PD-1 blockade therapy in melanoma mouse model, indicating that aspirin is potential to be used as an adjuvant in immune-based cancer therapy (Zelenay et al. 2015). Monokine induced by γ-interferon (CXCL-9) and interferon-γ-inducible protein-10 (CXCL-10) are important chemokines which recruit anti-tumor effector cells to tumors. Suppression of COX-induced PGE2 synthesis by aspirin (10 or 30 µM) promotes the secretion of CXCL-9 and CXCL-10 from MCF-7 and MDA-MB 231 cells stimulated by interferon γ (IFN- γ) (Bronger et al. 2012), thus enhances immune cell recruitment. Infiltration of T cell into tumor is restrained by vascular endothelial growth factor (VEGF) (Chen and Mellman 2013), while aspirin has been reported to suppress the expression of VEGF (Ding et al. 2014; Navone et al. 2018; Zhao et al. 2016). Hence, it is presumable that VEGF suppression induced by aspirin may promote T cell to penetrate the blood vessels and infiltrate into tumor. However, aspirin blocking the vascularization via inhibiting the expression of VEGF would decrease the blood circulation in tumor tissues and thus may impair the infiltration of T cells into tumor site. Thus, the net effect of aspirin on the infiltration of T cells into tumor microenvironment remains to be evaluated by more studies. Transforming growth factor β (TGF-β), a platelet-derived soluble factors, is a key molecule involved in platelet mediated cancer immune evasion by constraining the anti-tumor function of T cells and NK cells and protecting cancer cells from killing (Rachidi et al. 2017; Xu et al. 2018). As a well-known anti-platelet drug, aspirin combined with other anti-platelet counterparts (clopidogrel) contributes to adoptive T cell therapy for cancer and remarkably reduces tumor size in mouse models (Rachidi et al. 2017). Several studies indicate that aspirin alone or combined with other chemotherapeutic agents (cisplatin) could enhance the secretion of IFN-γ (Kumar and Singh 2012; Netea et al. 2000), a cytokine activating lymphocytes to eradicate cancer cells. The immune suppression role of myeloid-derived suppressor cells (MDSC), T regulatory cells (Treg) and macrophages, the major sources of inhibitory effectors in cancer immunity, may be also alleviated by aspirin. For instance, PGE2 production catalyzed by COX promotes the generation of MDSC, which suppresses anti-tumor immune cells but promotes the expansion of Treg (Liu et al. 2018). Thus, the anti-tumor immunity subverted by MDSC can be relieved by COX-2 inhibitors. Additionally, COX-2 inhibition also prevents the polarization of tumor-associated macrophages (TAMs) from an anti-tumor M1 macrophage to a pro-tumor M2 macrophage (Na et al. 2013).

Although several pioneering studies have already illustrated the promising role of aspirin in immunity against cancer, further investigations are indispensable to demonstrate that aspirin is a potent adjuvant in cancer immunotherapy and to explore the involved mechanisms.

Aspirin blunts the proliferation of cancer cells

Compared with other cancer hallmarks, the inhibition of proliferation is the most frequently reported mechanism for the ability of aspirin to inhibit cancer progression (Ding et al. 2014; Kumar et al. 2018; Li et al. 2016; Liu et al. 2019; Mitrugno et al. 2017; Schror 2011; Wu et al. 2017).

MAPK signaling is a critical molecular pathway that regulates the proliferation process of cancer cells. Ras, an important GTP-binding protein in MAPK signaling circuitry, has been reported as a target of aspirin. NSAIDS NS398 facilitates the inhibitory phosphorylation of Ser259 in c-Ras and thus blocks c-Ras from membrane recruitment, which means that the interplay between Ras and c-Ras is restricted and attenuated (Pan et al. 2008). Like NS398, aspirin and other NSAIDs, such as sulindac sulfide and indomethacin, also inhibit the binding of c-Raf to Ras and subsequently suppress the activation of ERK (Pan et al. 2008), resulting in the downregulation of multiple transcriptional factors such as myc, which promotes cell proliferation by upregulating cyclins and downregulating p21. Recently, aspirin (IC_{50} 4.38 mM) is reported to block the interaction between K-Ras and p110α, subsequently inhibits human uterine leiomyoma cell (GM10964) growth (Gao et al. 2017a). In addition, it is reported that compared with metformin or A769662, aspirin (2 mM) is a better AMPK activator when combined with multikinase inhibitor sorafenib. The combination of these two drugs enhances the BRAF/CRAF dimerization and concomitantly induces the hyperactivation of AMPK/ERK pathways in RAS-mutant cancers (Hammerlindl et al. 2018), which provides a novel strategy in cancer treatment.

PI3K signaling is another vitally important molecular pathway closely involved in cancer cell proliferation. Aspirin also inhibits the activity of PI3K/AKT signaling (Uddin et al. 2010). Interestingly, molecular pathological epidemiology studies suggest that the regular use of aspirin after diagnosis prolongs the survival of a subtype of CRC patients with mutation of phosphatidylinositol-4,5-biphosphate 3-kinase (PIK3CA), which encodes the catalytic subunit of PI3K (Grancher et al. 2018; Liao et al. 2012). It was recently discovered that aspirin is also able to restrict the growth of breast cancer with PIK3CA mutations through a COX-independent mechanism (Henry et al. 2017). As for the mechanism of aspirin specifically suppressing the proliferation of cancer cells harboring PIK3CA mutation, we speculate that PIK3CA would become a major driver gene if it mutated, thus inhibition of PIK3CA suppresses the proliferation of these cells, however, in cancer cells without PIK3CA mutation, PIK3CA is not a key gene to drive cancer proliferation, thus the effect of aspirin inhibiting PIK3CA will not be observed. Consistently, mutant PIK3CA is identified as one of the key driver genes in the progression of CRC (Huang et al. 2018). These studies imply that the mutation of PIK3CA is a marker that predicts whether aspirin is helpful in adjuvant cancer treatment.

In addition to MAPK and PI3K signaling, aspirin also targets other pathways and factors that promote the proliferation of cancer cells. PGE2 is reported to mediate proliferation, malignant transformation and progression of human hepatocellular carcinoma (Zang et al. 2017). It has been demonstrated that PGE2 regulates cell proliferation in human colon cancer cells via the PKA and PKB pathways (Kisslov et al. 2012). Moreover, PGE2 binds to EP2 and activates WNT/β-catenin signaling, which also boosts cancer growth (Gala and Chan 2015). Aspirin blunts COX-2, thereby reducing the synthesis of PGE2 and thus inhibiting the proliferation of cancer cells. In addition, aspirin obstructs the activation of NF-κB, resulting in the downregulation of various NF-κB regulated cytokines, such as interleukin-1 (IL-1), TNF and IL-6, which act as growth factors and boost the proliferation of cancer cells (Kawano et al. 1988; Osborn et al. 1989). Salicylate-mediated proliferation arrest is also related to the repression of proteins involved in cell proliferation and the cell cycle, including p70s6k, c-myc, cyclin D1, cyclin A, and proliferating cell nuclear antigen (Law et al. 2000). Another study conducted by Pathi et al. demonstrated that aspirin (5 or 10 mM) and salicylate restrict proliferation, survival and angiogenesis in colon cancer via the downregulation of specificity protein (Sp) transcription factors (Sp1, Sp3 and Sp4) and several Sp-regulated gene products promoting cell proliferation and growth, such as hepatocyte growth factor receptor (c-MET), VEGF and vascular endothelial growth factor receptor-1 (VEGFR1) (Pathi et al. 2012). Besides, platelets, promoting the upregulation and activation of the oncoprotein c-MYC and favoring the proliferation of SW480 cells and PANC-1 cells, can be restricted by aspirin (20 μM) (Mitrugno et al. 2017).

Aspirin impedes cancer invasion and metastasis

The epithelial-to-mesenchymal transition (EMT) plays a vitally important role in cancer invasion, migration and metastasis (Yeung and Yang 2017), and the dysregulation of WNT/β-catenin signaling contributes to cancer metastasis. Upon defeat of the WNT ligand, β-catenin ubiquitination and degradation is mediated by a destruction complex composed of axin, adenomatous polyposis coli (APC) and glycogen synthase 3β (GSK3β). Abnormal accumulation of β-catenin in the cytoplasm and nucleus caused by aberrant activation of WNT signaling is observed in the majority of CRCs (Perkins 2012) and is virtually intertwined with cancer metastasis (Li et al. 2014). The inactivation of protein phosphatase 2A (PP2A) induced by aspirin (from 8 to 5000 μM) in SW480 cells ultimately triggers the increased phosphorylation of amino acid residues (Se41 and Thr45) of β-catenin following the ubiquitination and degradation of β-catenin (Bos et al. 2006), thereby presumably intervening with EMT and hindering metastasis.

Aspirin treatment (2.5 mM) has been revealed to reduce E-cadherin repressor Slug and repress EMT and migration of K-ras-expressing non-small cell lung carcinoma A549 cell (Khan et al. 2016). It is also reported that aspirin inhibits EMT induced by IL-6 in a p53-dependent manner (Brighenti et al. 2016). C-myc expression induced by IL-6 accelerates the ribosomal biogenesis rate, which activates the ribosomal-Mdm2-p53 pathway and leads to p53 degradation. Devastation of p53 triggers E-cadherin downregulation and thus results in EMT (Brighenti et al. 2016). The therapeutic dosage administration of aspirin (100 μM and 500 μM) suppresses IL-6-induced c-myc transcription. Ribosomal protein S6, followed by c-myc RNA downregulation, decelerates rRNA maturation, thereby restricting the ribosomal biogenesis rate and causing p53 relief from Mdm2-mediated proteasome degradation. The accumulation of stabilized p53 profoundly contributes to EMT inhibition (Brighenti et al. 2016).

The extracellular matrix (ECM) and basement membrane are competent barriers that prevent tumor cells from metastasis. Nevertheless, metalloproteinases (MMPs) are a family of enzymes that can undermine these barriers and make it more convenient for tumor cells to leak into the circulation and subsequently undergo metastasis. Particularly, MMP-2 and MMP-9 degrade type IV collagen, the essential component of the basement membrane (Zeng et al. 1999). As reported in a study on prostate cancer, aspirin administration (5 mM) induces the downregulation of matrix MMP-9 and inhibits the activity of tissue inhibitors of metalloproteinase-1 (TIMP-1) in human prostate cancer cells (Shi et al. 2017), thus protecting the extracellular matrix and basement membrane from degradation. Additionally, aspirin (20 mM) is also reported to inhibit the expression of MMP-7 and MMP-12 in human bronchial cells stimulated with lipopolysaccharide (LPS) (Jiang et al. 2016). A recent study also shows that 600 μg/ml of aspirin administration restricts 143B osteosarcoma cell metastasis in mouse model through blocking STAT3 phosphorylation, reducing MMP-9 expression and inhibiting EMT (Han et al. 2019).

Additionally, the close relationship between platelets and cancer metastasis has been established since Armand Trousseau demonstrated in 1865 that thrombosis participates in cancer progression (Plantureux et al. 2018). On the one hand, platelets release factors that stimulate the EMT of cancer cells and thus facilitate cancer metastasis (Labelle et al. 2011). On the other hand, platelets can form a thick shield on the surface of cancer cells, which protects tumor cells from recognition by immune cells in the circulation during metastasis and seeding (Haemmerle et al. 2018; Quail and Joyce 2013). In addition, platelets help cancer cells attach to the endothelium and facilitate their extravasation and seeding (Xu et al. 2018). A low-dose aspirin regimen (75 mg/day) inhibits the activity of COX-1, thus preventing conversion from arachidonic acid to thromboxane A2 (TXA2), which is of profound importance in platelet activation and recruitment. In fact, inhibition of platelet COX-1 is a central mechanism in the anti-tumor effects of aspirin (Patrignani and Patrono 2016; Santilli et al. 2016). Randomized trials suggest that low-dose of aspirin (75 mg/day) reduces the risk of colorectal cancer and further benefits are not found on those who taking aspirin greater than 75 mg daily (Rothwell et al. 2010). Besides, a large-scale case–control study reports that the regular use of aspirin is associated with the reduction of distant metastasis but not regional spread (Algra and Rothwell 2012). Moreover, experimental researches also confirm that the inhibition of platelet by aspirin is of great importance in metastasis inhibition. It is reported that low-dose aspirin (20 mg/kg, p.o., once a day) disturbs the platelet–cancer cell-crosstalk and subsequently inhibits EMT of human colon cancer cells in mice (Guillem-Llobat et al. 2016). A recent in vitro study also shows that 100 μM of aspirin splits platelet–cancer cell interactions and prevents metastasis of breast cancer cells (Johnson et al. 2019). Accordingly, by inhibiting the function of platelets, aspirin use disturbs the platelet–cancer cell-crosstalk and renders tumor cells more exposed to the immune surveillance system (Rachidi and Metelli 2017), which block tumor metastasis in the circulatory system (Stegner et al. 2014).

Aspirin restricts angiogenesis

Angiogenesis is necessary for the growth of cancer and facilitates cancer metastasis. It has been demonstrated that the VEGF family and its cognate receptors play major roles in tumor angiogenesis (Ferrara et al. 2003). Additionally, many other mediators contribute to angiogenesis, such as angiopoietins and their receptors, platelet-derived growth factor and fibroblast growth factor (FGF2) (Maisonpierre et al. 1997; Ramjiawan et al. 2017).

The overexpression of COX-2 is frequently observed in many cancer types. COX overexpression not only promotes the proliferation and metastasis of cancer cells, but also contributes to tumor angiogenesis (Finetti et al. 2012; Howe et al. 2013; Huang et al. 2005; Tsujii et al. 1998). It has been proposed that COX-2 primarily regulates angiogenic factors in epithelial cells, and COX-1 is associated with angiogenesis in endothelial cells (Tsujii et al. 1998). Angiogenesis inhibition by aspirin is largely dependent on its effect on COX activity. For instance, aspirin (100 mM) inhibits the production of VEGF, TGF-β and FGF2 in HCA-7 cells, a colon cancer cell line that constitutively expresses COX-2 (Tsujii et al. 1998).

In addition to COX, NF-κB is also found to regulate VEGFR expression and modulates microvessel density in human CRC (Tsujii et al. 1998). Aspirin suppresses NF-κB activation and thus attenuates the expression of angiogenic factors mediated by NF-κB, such as monocyte chemotactic protein 1 (MCP-1) and VEGF, which profoundly contribute to angiogenesis restriction in cancer (Loch et al. 2001). Additionally, a recent study shows that aspirin (2 or 5 mM) inhibits VEGF expression via enhanced histone methylation of VEGF promoter in nasal-type natural killer/T cell lymphoma (NKTCL) SNK-6 cells (Zhang et al. 2018).

Aspirin also restricts angiogenesis through VEGF-independent manners. It is reported that aspirin treatment (1 or 2.5 mM) inhibits tumor-cell induced angiogenesis in breast cancer via blocking paracrine–autocrine signaling crosstalk between tumor cells and endothelial cells (Maity et al. 2019). Another research also indicates that both low (100 mg/kg) and high (400 mg/kg) doses of aspirin inhibit the expression of p-mTOR and HIF-1α and then restrain angiogenesis in murine hepatocarcinoma and sarcoma models (Zhao et al. 2016).

Aspirin breaks resistance to cell death and induces apoptosis in cancer

The induction of apoptosis is also a well-documented mechanism related to the anti-cancer activity of aspirin. It has been revealed that aspirin induces apoptosis in cancer cells in many cancer types, such as colon cancer, breast cancer and gastric cancer (Choi et al. 2013; Stark et al. 2001; Wong et al. 1999).

The main metabolite of aspirin, salicylate (2 mM) is able to depolarize the mitochondrial membrane and inhibit Ca^{2+} influx in HT29 cells (Nunez et al. 2006), which may induce apoptosis and restrict cell proliferation. And aspirin (10 mM) induces the release of cytochrome *c* from mitochondria and activation of caspase-9 and -3, resulting in apoptosis in cancer cells (Pique et al. 2000).

The pro-apoptotic property of aspirin is also associated with the crosstalk between the NF-κB pathway and nucleoli. Aspirin and other stimuli result in the nucleolar sequestration of Rel-A (p65) (Thoms et al. 2010). Meanwhile, nucleolar residency of Rel-A forces nucleophosmin (NPM) to retranslocate into the cytoplasm and bind with Bcl-2-associated X protein (Bax), ultimately inducing mitochondria-mediated apoptosis (Thoms et al. 2010).

It has also been found that B-cell lymphoma 2 (Bcl-2) is a novel target molecule of aspirin that induces apoptosis. A previous research study suggested that aspirin (5 mM) induces the phosphorylation and nuclear translocation of Bcl-2 in MCF-7 breast cancer cells, which contributes to apoptosis. Upon knockdown of the expression of Bcl-2, aspirin treatment fails to prevent proliferation, whereas the overexpression of Bcl-2 enhances aspirin-induced apoptosis (Choi et al. 2013). This unexpected result suggests that Bcl-2 is necessary for the onset of aspirin-induced apoptosis. Recently, it is reported that aspirin downregulates Bcl-2 and induces apoptosis in several types of cancer cells, such as cholangiocarcinoma cells (KKU-214), multiple myeloma cells (MM1.S and RPMI-8226), hepatocellular carcinoma cells (Hep-2) and breast cancer cells (Boueroy et al. 2017; Ding et al. 2014; Jin et al. 2018; Wu et al. 2017).

Finally, COX/PGE2 upregulates the transcription of anti-apoptosis genes, for instance, Bcl-2 (Sheng et al. 1998); thus, the inhibition of COX by aspirin also triggers apoptosis. Additionally, COX inhibition induced by aspirin triggers the accumulation of arachidonic acid. The remarkable elevation of arachidonic acid prominently promotes the conversion of sphingomyelin to ceramide, which is a known compound that mediates apoptosis (Chan et al. 1998).

Aspirin restores growth suppressor signaling

P53 is a canonical growth suppressor protein that profoundly limits excessive cell growth. Upon DNA damage, p53 can activate p21 and Bax and thus stop the cell cycle and trigger DNA damage repair or induce apoptosis when the repair of damaged DNA fails (Harris and Levine 2005; Slee et al. 2004). The research conducted by Alfonso et al. demonstrated that acetylate p53 at lysine 382 induced by aspirin (100 mM) enhances its DNA-binding activity and increases the expression of its target genes, such as $p21^{CIP1}$ and Bax in a human breast cancer cell line (Alfonso et al. 2009). In another study, it was demonstrated that aspirin acetylates p53 and induces $p21^{CIP1}$ in colon cancer cells (Ai et al. 2016). Moreover, it was also shown in this study that aspirin could acetylate both wild-type and mutant p53, and the acetylation of mutant p53 partially restores its DNA-binding ability in certain cases, suggesting the possibility that aspirin suppresses cancer growth through restoration of the functions of mutant p53. Besides, the epigenetic regulation mediated by aspirin, such as histone modification, targeting DNA methylation may also help to re-activate the expression of other growth suppressor genes and restore the growth control mechanisms (Yiannakopoulou 2014).

Aspirin attenuates the replicative immortality of cancer cells

It is well known that telomerase activation is critical for the replicative immortality of cancer cells by maintaining the telomeres to sustain division and proliferation (Hannen and Bartsch 2018). It has been revealed that telomerase activity was inhibited in colon carcinoma cell lines after treatment with aspirin (0.5 mM) and other NSAIDs, and the expression of human telomerase reverse transcriptase (hTERT), an essential subunit of telomerase, was also suppressed at the transcription level (He et al. 2006). This study suggests that aspirin attenuates the replicative immortality of cancer cells by directly inhibiting the transcription of hTERT.

Aspirin possibly inhibits the genome instability of cancer cells

Genome instability facilitates gene mutations and thus promotes carcinogenesis and the progression of cancer. Currently, the question of whether aspirin could actually affect the genome instability of cancer cells has not yet been explored. However, because aspirin can acetylate p53 and enhance its activity and because p53 serves as a guardian of the genome, the activation and restoration of p53 by aspirin in certain cases might enhance its capability of DNA damage repair or induce apoptosis if necessary, possibly retrieving gene stability as a result.

In addition to p53, aspirin acetylates many other nuclear proteins, such as histones, and also acetylates DNA or RNA (Lai et al. 2010; Pinckard et al. 1968). The acetylation of these nuclear molecules might possibly regulate genome instability. It also has been suggested that aspirin and other NSAIDs prevent cancer potentially through regulating histone modification (Yiannakopoulou 2014). However, a recent study investigating aspirin-mediated acetylation showed that although aspirin (5 mM) induces widely acetylation of histones, only less than 1% potential sites actually acetylated at any given time (Tatham et al. 2017), which suggests that the effect of aspirin-mediated histone acetylation may not be sufficient to have a lasting effect on DNA binding and produce biological effects. Hence, the effects of the chemical acetylation property of aspirin on the nucleus and on the maintenance of genome stability are topics that deserve further detailed studies.

Some other studies indicate that aspirin is a potential agent to protect and repair DNA damage (Chen et al. 2009; Dibra et al. 2010; Goel et al. 2003) as well as decelerate the accumulation of mutations (Kostadinov et al. 2013), which contribute to genomic stability and inhibition of cancer initiation and progression. Chen et al. have found that aspirin at 0.25–2 mM inhibits DNA breaks and reduces hydroxyl radical formation caused by peroxynitrite (Kostadinov et al. 2013). Besides, Geol et al. confirm that treatment with 1 and 5 mM aspirin obviously increases the expression of DNA mismatch repair proteins hMLH1, hPMS2, hMSH6 and hPMS2 in human HCT116 + chr3 and SW480 colorectal cancer cell lines (Goel et al. 2003). Another research also reports that 1 mM aspirin treatment over 48 h increases the expression DNA repair protein XRCC3 (Dibra et al. 2010). In addition, patients of Barrett's esophagus who use aspirin long term have reduced rate of acquisition of somatic genomic abnormalities compared to those who do not use aspirin (Kostadinov et al. 2013).

Aspirin universally inhibits the activation of and crosstalk between signaling pathways

Although the precise mechanisms by which aspirin exerts its anti-cancer effects are still not completely elucidated, two major models are proposed to explain the mechanisms of aspirin action, namely, COX-dependent and COX-independent mechanisms (Alfonso et al. 2014; Thun et al. 2012). The observations that COX is usually overexpressed in various cancer types and participates in cancer progression strongly support the idea that the inactivation of COX is an important mechanism by which aspirin exerts its anti-cancer effect (Guillem-Llobat et al. 2014; Thun et al. 2012). However, a study elucidated that the anti-inflammatory effects of aspirin and sodium salicylate were also discovered in COX 2- and NF-κB (p105)-knockout mice (Weissmann et al. 2002). Besides, studies have revealed that aspirin inhibits the proliferation of COX-null transformed cells (Zhang et al. 1999), and the observation that the growth inhibitory effect of aspirin cannot be reversed by the addition of PGEs (Zhang et al. 1999). These studies strongly suggest that other COX-independent mechanisms exist that explain the anti-cancer properties of aspirin. In fact, aspirin might simultaneously exert its anti-cancer effect via multiple mechanisms in most conditions, considering the crosstalk between the targets of aspirin (Fig. 2).

COX-2 overexpression in cancer cells elevates the synthesis of PGH2, which is further catalyzed by PGES and converted to PGE2. PGE2 is secreted to the outside of the cancer cells and subsequently binds to its receptors (EP1, EP2, EP3 and EP4) in a paracrine or autocrine manner, which ultimately promotes cancer progression by activating downstream signaling pathways, such as NF-κB, MAPK, PI3K/AKT, PKA and β-catenin signaling (Banu et al. 2009; Cheng et al. 2014; Majumder et al. 2018; O'Callaghan and Houston 2015; Parida et al. 2016; Shehzad et al. 2015; Zhang et al. 2016b) (Fig. 2). Interestingly, many of these signaling pathways activated by PGE2 could reversely promote the transcription of COX-2 in various cancer types. For instance, the observation that NF-kB activation promotes the transcription of COX-2 has been well documented (Gong et al. 2014; Wang et al. 2017). In addition, MAPK signaling activation of targets such as p38 and ERK also contributes to the elevated transcription of COX-2 (Sun et al. 2010; Syeda et al. 2006). The promoter of the COX-2 gene contains β-catenin recognizing sites, and the activation of WNT/β-catenin signaling enhances the transcription of COX-2 in gastric cancer and colon cancer (Hsu et al. 2017; Nunez et al. 2011). Besides, activation of cAMP response element-binding protein (CREB) induced by PKA signaling directly triggers transcription of COX-2 (Ruan et al. 2012). Moreover, CREB suppresses the expression of microRNAs (miR101 and miR199a) targeting COX-2 and upregulates the expression of COX-2 at the post-transcription level (Sun et al. 2014). Meanwhile, CREB inhibits 15-prostaglandin dehydrogenase (15-PGDH), a prostaglandin-degrading enzyme, and upregulates PGE2 (Castro-Sanchez et al. 2013; Pino et al. 2005; Tsatsanis et al. 2006). By the way, in addition to PIK3CA mutation, 15-PGDH expression is now considered as another biomarker to indicate whether aspirin is efficient to prevent cancer (Fink et al. 2014). All studies mentioned above suggest several positive feedback pathways between COX-2/PGE2 and the signaling pathways associated with cancer progression. Because crosstalk occurs among these signaling pathways, activation of one of them in certain cancer types could trigger these positive circuits. However, aspirin inhibits the activity of COX-2 and thus blocks the

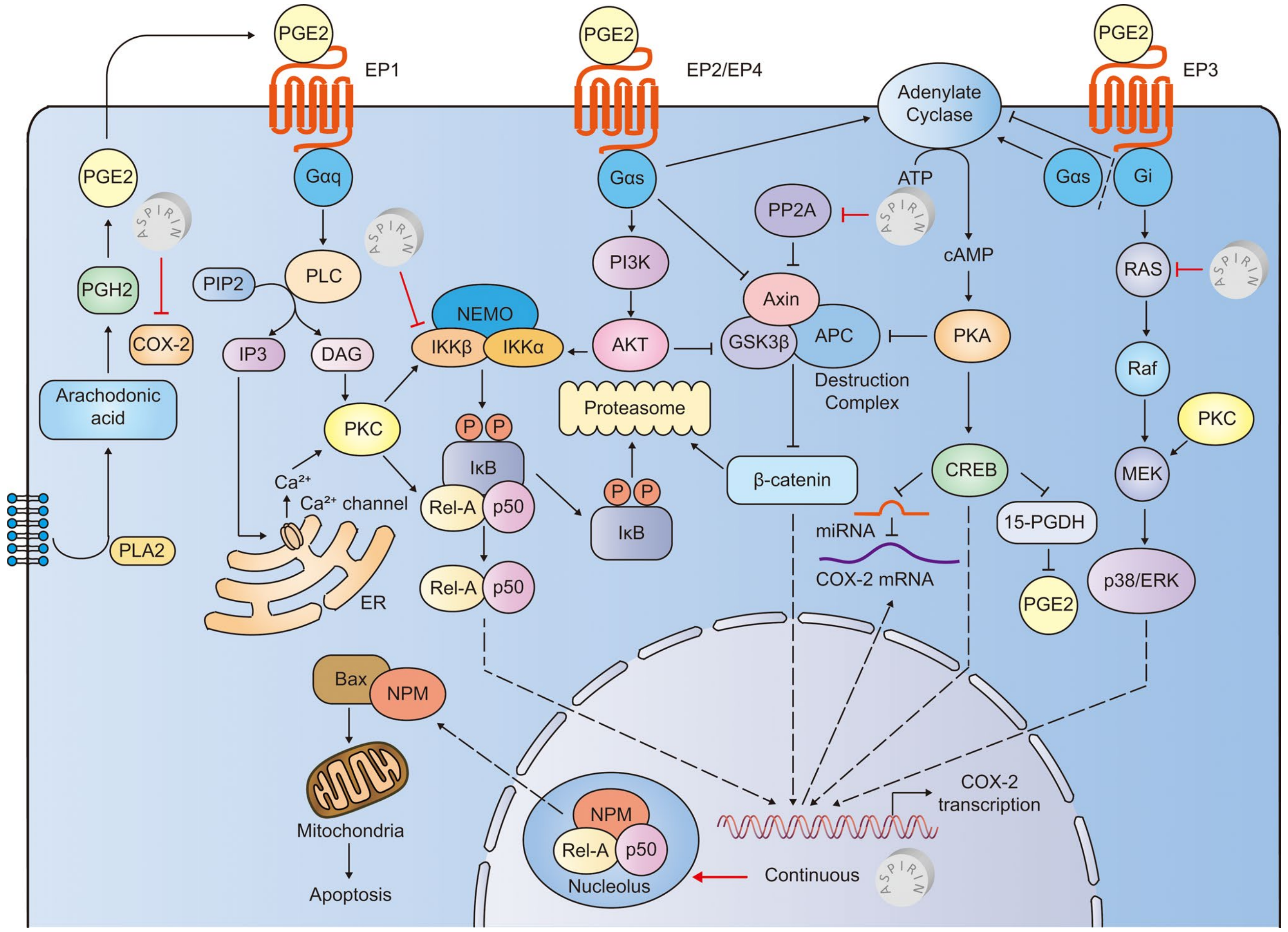

Fig. 2 Crosstalk between the targets of aspirin. Secreted PGE2 binds to its receptors (EP1, EP2, EP3 and EP4) in a paracrine or autocrine manner and activates downstream signaling pathways, such as NF-κB, MAPK, PI3K/AKT, PKA and β-catenin signaling. Activations of these signaling pathways in return enhance the expression of COX-2, which further contributes to production of PGE2. Aspirin regulates multiple signaling pathways, decreases the transcription and activation of COX-2, thereby blocks the generation of PGE2

generation of PGE2, regulating the activation of many signaling pathways and decreasing the transcription of COX-2. In summary, aspirin is a master inhibitor of oncogenic signaling pathways by inhibiting the activation of and crosstalk between these pathways.

Adverse effects of aspirin

As one of the most commonly used non-steroid anti-inflammation drugs, on the one hand, aspirin serves as a chemopreventive reagent in cancer and cardiovascular diseases, on the other hand, it also brings several troublesome adverse effects to restrict the wide application of this compound.

Gastrointestinal toxicity is one of the adverse effects of aspirin. The chronic use of aspirin is well known to be associated with upper gastrointestinal injury (Lavie et al. 2017). Epigastric stress, ulceration and hemorrhage may torture patients and terminate aspirin treatment. Mechanically, prostacyclin (PGI2) restrains secretion of gastric acid, whereas PGE2 and PGF2α stimulates synthesis of protective mucus in stomach and small intestine. Aspirin blocks the synthesis of these prostaglandins and leads to increased gastric acid secretion and attenuates mucus protection, hence renders the gastrointestinal tract more vulnerable. Additionally, aspirin is acidic and it can easily cross into mucosal cell at gastric pH and directly cause damage to the cells. Thus, a proton pump inhibitor (PPI) is eligible to be a concomitant reagent to relief the dyspepsia induced by aspirin (Dahal et al. 2017). Apart from the upper segment, the lower gastrointestinal tract also suffers from the adverse effects of aspirin. A recent report has indicated that long-term use of low-dose aspirin leads to various lesions in the lower gastrointestinal tract, such as erosions, ulcers and diverticular hemorrhage (Sostres and Lanas 2015).

Bleeding caused by inhibiting TXA2 and blocking platelet aggregation and aspirin exacerbated respiratory disease (AERD) characterized by hypersensitivity and encompass asthma and chronic rhinosinusitis with nasosinusal polyposis are other frequently reported adverse effects caused by aspirin (Pavon-Romero et al. 2017). The detailed adverse effects of aspirin are also reviewed clearly by Hui et al. (2018b).

Novel derivatives of aspirin have been already developed in order to reinforce the anti-cancer effects and attenuate the adverse effects. For instance, phospho-aspirin, which possesses a modified carboxyl group, has lesser gastrointestinal toxicity but performs more potently on tumorigenic inhibition (Huang et al. 2011).

Conclusion and perspectives

Aspirin, one of the most frequently used nonsteroidal anti-inflammatory drugs in the clinic, has been demonstrated as a promising preventive and adjuvant therapeutic agent in colorectal cancer (Algra and Rothwell 2012; Cuzick et al. 2009). Besides, it has been reported that aspirin also exerts this anti-cancer effect in other cancer types, such as liver cancer, prostate cancer and breast cancer (Hua et al. 2018b). However, some clinical observational studies provide evidence that aspirin use shows no benefit in cancer prevention and even causes healthy problems (Kim et al. 2018; McNeil et al. 2018a, b, c; Okada et al. 2018). Thus, the detailed effects of aspirin remain to be verified through more large-scale clinical trials in the future. Current studies have revealed that aspirin regulates almost all of the hallmarks of cancer. Aspirin not only suppresses the bioactivities of cancer cells themselves by inhibiting proliferation, metastasis and metabolism reprogramming thereby promoting apoptosis (Khan et al. 2016; Mitrugno et al. 2017; Spitz et al. 2009; Zimmermann et al. 2000), but also deteriorates the tumor microenvironment to prevent cancer progression, for example, by inhibiting tumor-associated inflammation and angiogenesis and reversing anti-cancer immunity escape (Borthwick et al. 2006; Ma et al. 2015; Zelenay et al. 2015). Additionally, aspirin inhibits cancer progression via an extra cancer tissue process. Aspirin blocks the activation of platelets, which favors cancer growth and metastasis (Haemmerle et al. 2018). In terms of the molecular mechanism, the anti-cancer effect of aspirin is dependent on its roles in inhibiting several master signaling pathways that promote cancer progression, such as COX/PGE2, NF-κB, PI3K/AKT/mTOR, WNT/β-catenin and MAPK signaling (Alfonso et al. 2014; Hua et al. 2018a).

In addition, considering the important roles of microbiota in the tumorigenesis and progression of colorectal cancer (Mandal 2018; Zou et al. 2018), further studies should be conducted to detect whether the anti-cancer effect of aspirin in colorectal cancer is partially dependent on its ability to modify gut microbiota. It has been reported that NSAIDs administration is closely associated with distinct microbial populations (Rogers and Aronoff 2016), whereas gut microbiota mediates the suppression of anti-tumor immunity via COX–PGE2 pathway in obesity-associated liver cancer (Loo et al. 2017). Thus, it is presumable that aspirin, which inhibits its COX activity and restrains PGE synthesis, might inhibit the gut microbiota-associated carcinogenesis and cancer progression.

Moreover, animal and clinical studies have shown that aspirin increases the chemotherapeutic effect in colon cancer (Lee and Gibbs 2015; Ng et al. 2015), and recent studies also suggest that aspirin increases the effect of immune-checkpoint blockades on certain cancer types (Page et al. 2014; Sharma and Allison 2015; Zelenay et al. 2015). Therefore, the combined use of aspirin with other therapeutic methods such as tumor-targeting therapy is a novel direction for extending the application of aspirin in cancer prevention and therapy. Although the acetylation role of aspirin was discovered as early as the 1970s when it was revealed to inhibit the COX enzyme, it appears that the acetylation effect of aspirin has been ignored for a long period of time. Current studies suggest that aspirin can acetylate hundreds or thousands of proteins, including some nuclear proteins (Alfonso et al. 2014; Lai et al. 2010; Pinckard et al. 1968). In addition to the acetylation of proteins, aspirin may also acetylate the biological consequences of RNA and certain small-molecule metabolites, such as acetyl-CoA (Alfonso et al. 2014; Moss 2013). Thus, the identification of novel targets of aspirin, especially molecules other than proteins, offers a promising direction for studying the mechanisms of action of aspirin.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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