Published in final edited form as:

Curr Angiogenesis. 2013 September 1; 2(2): 135–142. doi:10.2174/2211552802999140131105947.

The influence of Cox-2 and bioactive lipids on hematological cancers^a

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Abstract

Inflammation is implicated in the progression of multiple types of cancers including lung, colorectal, breast and hematological malignancies. Cyclooxygenases (Cox) -1 and -2 are important enzymes involved in the regulation of inflammation. Elevated Cox-2 expression is associated with a poor cancer prognosis. Hematological malignancies, which are among the top 10 most predominant cancers in the USA, express high levels of Cox-2. Current therapeutic approaches against hematological malignancies are insufficient as many patients develop resistance or relapse. Therefore, targeting Cox-2 holds promise as a therapeutic approach to treat hematological malignancies. NSAIDs and Cox-2 selective inhibitors are anti-inflammatory drugs that decrease prostaglandin and thromboxane production while promoting the synthesis of specialized proresolving mediators. Here, we review the evidence regarding the applicability of NSAIDs, such as aspirin, as well as Cox-2 specific inhibitors, to treat hematological malignancies. Furthermore, we discuss how FDA-approved Cox inhibitors can be used as anti-cancer drugs alone or in combination with existing chemotherapeutic treatments.

Inflammation and cancer

Inflammation is a critical step during the immune response, which can be triggered by foreign pathogens, injury or trauma. Inflammation is characterized by the four cardinal signs, *rubor, dolor, calor and tumor*. Regulating the beginning of inflammation, as well as its resolution, is a fundamental process required to prevent disease while maintaining homeostasis. A deficient inflammatory response will hinder the activation of the immune system, in turn aiding pathogen infiltration and preventing tissue healing. Alternatively, uncontrolled or chronic inflammation can lead to disease such as autoimmune disorders and cancer (1).

^aThis work was supported by NIH grants ES01247, T32 DE007202 and AI103690

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Inflammation and cancer share pathological characteristics that include increased blood flow, cellular recruitment and tissue remodeling (2,3). Inflammation is implicated in the progression of multiple types of cancers including lung, colorectal, breast, head, neck, and hematological malignancies (4–11). Understanding and more importantly, regulating inflammation is a vital component for the development of novel and efficient cancer therapies.

Cyclooxygenases (Cox) are important enzymes involved in the regulation of inflammation. Cox-1 and Cox-2 isoforms are associated with the production of proinflammatory prostanoids including prostaglandins (PGs) and thromboxanes (TXs) (12). Cox-1 is constitutively expressed and regulates basal prostanoid levels. Conversely, the inducible isoform, Cox-2, upregulates prostanoid production during inflammatory conditions (12). Because of its proinflammatory properties, Cox-2 is considered an oncogene. Increased Cox-2 expression is associated with a poor cancer prognosis (5–8).

Following cleavage of arachidonic acid from the cell membrane, Cox-2 regulates the production of PGH_2 , a major intermediate from which multiple PGs and TXs are biosynthesized. PGE_2 , a well-studied prostaglandin produced from PGH_2 , is a potent proinflammatory lipid molecule capable of increasing blood flow and cell permeability into the tissue (13). Increased Cox-2 and PGE_2 production are associated with carcinoma progression and metastasis in hematological malignancies, as well as lung, colon and gastric carcinomas among others (9–11,14,15). Given the link between Cox-2, its bioactive lipid-products and cancer, both selective and non-selective Cox inhibitors are being investigated in the clinic as potential treatments for cancer.

In addition to the proinflammatory PGs and TXs, arachidonic acid is metabolized via an alternative enzymatic pathway mediated by acetylated Cox-2 and lipoxygenases (LOXs). LOXs are an enzymatic family responsible for the production of leukotrienes (LTs) and lipoxins (16,17). Lipoxins are a relatively new set of molecules that belong to a class of lipid mediators called specialized proresolving mediators (SPM) (18). SPM are thought to have anti-cancer properties because, unlike their biosynthetic prostanoid counter parts, SPM help arrest and resolve inflammation (16,19). In this review, we will discuss the potential of Cox-2 and its bioactive lipid derived products as therapeutic targets to treat hematological malignancies. Figure 1 outlines the potential mechanism by which Cox-2 inhibitors decrease inflammation and decrease cancer risk.

Inhibiting Cox-2 in hematological malignancies

The most recent survey by the CDC and the National Cancer Institute, categorize hematological malignancies among the top 10 most predominant cancers in the US. In 2008, 54,576 people died from a hematologic cancers and 124,556 more were diagnosed with a form of cancer in their blood, bone marrow or lymph node (20,21). This is a great health concern at a national and global scale. Interestingly, hematological malignancies generally express high levels of Cox-2 (22–26). Elevated Cox-2 expression is correlated to poor prognosis and decreased survival in many types of cancers (22–25). Cox-2 selective inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) have important anti-

inflammatory properties. NSAIDs include both Cox-2 selective inhibitors (i.e. meloxicam, celecoxib) and non-selective inhibitors (i.e. aspirin, indomethacin, ibuprofen). Both Cox-2 selective inhibitors and NSAIDs, possess pro-apoptotic and anti-proliferative properties and thus have anti-carcinogenic properties.

Studies performed in our laboratory demonstrated that healthy human B cells do not express Cox-2 under resting conditions. However, B cells increase Cox-2 expression upon mitogen activation (27,28). Furthermore, we and others have shown that hematological malignancies such as chronic lymphocytic leukemia (CLL) cells express high levels of Cox-2, which promotes cell survival (22,29). Foremost, Cox-2 inhibitors, such as indomethacin, celecoxib (Celebrex), SC-58125 and OSU03012 inhibit the Cox-2-mediated pro-survival mechanisms in multiple malignancies, including hematological cancers (22,29–31). Chandramohan and colleagues demonstrated that Cox-2 overexpression provides anti-apoptotic properties to chronic myeloid leukemia cells (CML). By overexpressing Cox-2 in K562 cells, Chandramohan *et al.* found that the CML cells are less susceptible to gallic acid-induced apoptosis, an effect attributed in part to increased expression of Bcl-2 and decreased of cytochrome c release (32). Other NSAIDs, such as aspirin, are reported to have similar pro-apoptotic effects on CLL cells. Iglesias-Serret *et al.* have shown that aspirin-induced apoptosis in primary CLL and leukemia Jurkat T cells is regulated by the Bcl-2 family members Mcl-1 and Noxa (33).

Besides their pro-apoptotic properties, Cox-2 inhibitors also hold promise as cancer therapeutics as they decrease cell proliferation. Sobolewski *et al.* have shown that Cox-2 specific inhibitors promote a cytostatic state in CML and acute myeloid lymphoma (AML) cells. Nimesulide, NS-398 and celecoxib, decrease proliferation and induce cell cycle arrest at the G₀/G₁ phase by downregulating the expression of c-Myc and p27 (34). These findings are in support of previous reports in which Cox-2 inhibitors such as, indomethacin, celecoxib and Dup-697, decreased proliferation, promote cell cycle arrest and induce apoptosis in both primary CML cells, as well as CML cell lines (35–38). Cox-2 specific inhibitors such as celecoxib and NS-398 also decrease malignant cell growth and proliferation in models of non-Hodgkin's lymphomas and multiple myelomas, both *in vitro* and *in vivo* (39,40). Naturally-occurring small molecules such as quercetin and decursin, which are not NSAIDs, have also been shown to target and inhibit Cox-2 function (41–43). Ahn and colleagues showed that decursin, similarly to the Cox-2 inhibitors NS398 and celecoxib, reduced Cox-2 expression in the CML cell line KBM-5. The downregulation of Cox-2 in CML leads to cell cycle arrest and increases apoptosis (43), an effect that is consistent with decursin as an anti-carcinogenic agent. Therefore, inhibiting Cox-2 decreases malignant cell proliferation, an important component during cancer treatment.

In addition to their pro-apoptotic and anti-proliferative effects, Cox-2 inhibitors also possess anti-angiogenic properties. An inflammatory tumor microenvironment promotes angiogenesis and growth, thus leading to malignancy progression. Angiogenesis is dependent on multiple variables including key cell growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Cox-2 promotes angiogenesis by increasing VEGF and FGF production (9,44). In a melanoma murine model, Valcarcel *et al.* have shown that tumor growth and metastasis are dependent on VEGF

signaling. Most importantly, the Cox-2 inhibitor, celecoxib, blocked tumor metastasis *in vivo* (45). These observations complement previous clinical studies in which celecoxib in combination with chemotherapy, decreased the circulating serum levels of VEGF (46). A report by Chien *et al.* shows that in acute myeloid leukemia (AML), VEGF-C increases Cox-2 expression via JNK signaling. Consequently, higher Cox-2 activity increases production of proinflammatory prostaglandins, which in turn promote angiogenesis (47). These findings are intriguing, as they may suggest a positive feedback mechanism between Cox-2 and VEGF production. Further analyses are required to better understand the role of Cox-2 during angiogenesis. However, the findings discussed here, firmly support the translational power of Cox-2 inhibitors as potential cancer therapeutics.

Using Cox-2 inhibitors in the clinic

Given the pro-oncogenic properties of Cox-2, there is much interest in the development of therapies targeting Cox-2 during cancer progression (10,24). NSAIDs can lower the risk for colon, breast, esophagus and stomach cancer (48). Furthermore, multiple population-study reports support NSAIDs as potential agents to treat hematological malignancies. In a case-control study, Pogada and colleagues found that use (4 weeks for 2–10 years) of NSAIDs (most commonly used being ibuprofen, naproxen and piroxicam) decreased the risk of AML by 50% (49). More recently, a population study performed by Weiss *et al.* pooled 169 acute leukemia patients and compared them to 676 controls. Based on a comprehensive epidemiological questionnaire, Weiss reported that the regular use of aspirin (>3 times/week) over a 12-year period provided a protective effect against hematological malignancies. More specifically, aspirin intake strongly decreased the risk for developing acute lymphoblastic leukemia (ALL) and moderately decreased the risk for AML (50). An additional population-based case-control study by Ross and colleagues, analyzed the effects of NSAIDs in 670 newly diagnosed AML and CML patients. Regular-dose aspirin intake (1 × 325 mg table/week for 1 year) was found to decrease the risk of myeloid leukemia by 41% in women but not in men (51).

Interestingly, not all NSAIDs have protective effects against cancer. Some NSAIDs have been linked to increased risk for hematological malignancies. In a study by Vinogradova *et al.* it was found that use of Cox-2 inhibitors (mostly rofecoxib, celecoxib and meloxicam) increased the risk for hematological malignancies by 18% if taken short-term (1 prescription for 3–12 months) or up to 47% on long-term users (1 prescription for 2 years) (52). This is in contrast to previous studies and although Vinogradova's study used a large cohort that included 88,125 cancer patients, hematological malignancies were not the only focus of their study, thus their data is derived from a limited number of subjects with hematological cancers. The group of Walter and colleagues performed an additional population study to measure the effects of aspirin and non-aspirin NSAIDs specifically on hematological malignancies. Using 64,839 subjects as their sample population, the team found that high use (4 days/week for 4 years) of acetaminophen increased the risk of hematologic malignancies, myeloid neoplasm, mature B-cell neoplasm, but not chronic lymphocytic leukemia/small lymphocytic lymphoma (53). A different study by Weiss *et al.* also found that even a single use of acetaminophen increased the risk of ALL and AML and continued usage by 53% (50). In addition, acetaminophen also increased the risk for AML

and CML in women independently of the dose or duration of acetaminophen intake (51). Two other population-based case-control studies by Chang and colleagues reported on the contrasting outcomes of different NSAIDs, particularly acetaminophen and aspirin (54,55). The authors reported that acetaminophen increased the risk of Hodgkin's lymphoma by 72%. On the other hand, taking aspirin regularly (2 times of 325 mg tablets/week) reduced lymphoma incidence by 40% (54), and by 30% in subjects taking low-dose aspirin (> 2 times of 75, 100, or 150 mg tablets/month) (55). Even though these population-based studies show promising correlations between NSAID use and decreased hematological malignancies, it is important to acknowledge that many are limited by the availability of detailed patient information, size of the population studied and ability to perform long-term patient progress.

It is safe to say that the effects of the NSAIDs on hematological malignancies are far from uniform. Aspirin's protective properties are strongly contrasted by acetaminophen's enhanced risk for malignancies, while ibuprofen, for example, has been shown to have no effect on the incidence of hematological malignancies (51,53). Considering the specific cancer-responses seen to different kinds of NSAIDs, detailed examination of the molecular mechanisms responsible for their effects will allow for the development of improved therapeutic treatments.

Alternative use of Cox-2 inhibitors

Current approaches to treat hematological malignancies include radiotherapy and chemotherapeutic agents (56–58). Nevertheless, traditional therapies are not always sufficient. Gemtuzumab ozogamicin and imitinib, are two examples of commonly used treatments against AML and CML, to which patients develop resistance and suffer relapse (59–61). Cox-2 inhibitors are viable therapeutic alternatives to improve cancer treatment efficacy. Already, Cox-2 inhibitors, such as celecoxib, have shown protective effects against the development of colorectal cancer (62,63). Other Cox-2 specific inhibitors, including celecoxib and rofecoxib, have also been reported to minimize the risk for lung cancer (64). Nevertheless, the use of selective Cox-2 inhibitors, particularly at high concentrations, can lead to serious cardiovascular complications (65).

A promising approach involves the inclusion of NSAIDs to already existing chemotherapeutic treatments. Puhlmann and colleagues have shown that using meloxicam, a Cox-2 specific inhibitor, along with the chemotherapeutic agent, doxorubicin, decreases malignant cell growth and proliferation of hematological malignancies (66). In their study, Puhlmann *et al* showed a decreased proliferation by 30% in AML, and 78% in HL-60 cells, which were treated with meloxicam and doxorubicin. Interestingly, expression of the multidrug transporter MDR1, which is responsible for multidrug resistance in AML patients, was downregulated by meloxicam treatment (66). The clinical chemotherapeutics properties of meloxicam have also been reported in other types of cancers. A study by Suzuki *et al*. showed that non-small lung carcinoma patients given a combined chemotherapeutic treatment consisting of paclitaxel weekly, for 3 weeks with carboplatin on day 1, and a daily dose (10 mg/day) of meloxicam have a 43% improved treatment response (67). Meloxicam

(10 mg/day for a median period of 20 months) has also been used to effectively decreased the size of extra-abdominal desmoid tumors (68).

Importantly, some Cox-2 inhibitors have the capacity to target malignant cells, while not adversely affecting normal cells. Secchiero *et al.* have shown that the Cox-2 inhibitor, NS-398 and DuP697, promote apoptosis in B-CLL cells, but not in healthy cells. Furthermore, the chemotherapeutic agent chlorambucil in combination with NS-398 increases B-CLL cell death (29). Jamshidi *et al.* also reported that using 1,25-dihydroxyvitamin D3, the active form of vitamin D, along with indomethacin and aspirin, enhances human myeloid leukemia cell differentiation while decreasing cell proliferation. These synergistic effects are seen in primary AML as well as HL-60, THP-1 and U937 cell lines (69). Therefore the use of Cox-2 inhibitors in combination with established cancer therapies holds great promise as a novel alternative strategy to treat cancer.

Using aspirin to treat cancer

Aspirin is one of the most promising NSAIDs as a potential anti-cancer drug. Aspirin is a traditional and time-honored anti-inflammatory drug to reduce pain, fever, and even the risk for cardiovascular disorders. Aspirin is an irreversible non-specific Cox inhibitor that acetylates serine-530 within the Cox-2 active site, thus transforming Cox-2 enzymatic properties (70). A plethora of evidence exists demonstrating that aspirin consumption has beneficial effects as a treatment for many types of cancers, including hematological malignancies (71,72).

Early reports by Kasum and colleagues found that aspirin use (2/week) in a cohort of 28,224 postmenopausal women, decreased the risk of developing leukemia (including AML, CLL and CML) by 65% (73). Some of the most striking and latest reports have shown that regular aspirin intake has a strong protective influence against colorectal and other solid cancers. Rothwell and colleagues reported that high-dose (500 mg/day) aspirin intake lowers the risk of colorectal cancer by 24% and improves patient survival by 35%. Interestingly, long-term (5years) aspirin use reduces the risk of proximal colon cancer by 70% (74). Considering the previously discussed role of Cox-2 in angiogenesis, aspirin's long-term protective effects are attributed in part to decreased tumor metastasis (75). In a later population-study consisting of 17,285 patients from the United Kingdom, Rothwell *et al.* observed that long-term (5years) daily aspirin consumption (75 mg/day) decreases the risk of metastasis of colorectal and adenocarcinomas as well as the incidence of cancer-associated death (75). These large population-studies provide another set of strong evidence highlighting the anti-carcinogenic properties of aspirin on multiple types of malignancies. Better understanding the properties and mechanism(s) responsible for aspirin's beneficial effects are necessary in order to develop better treatments against cancers, such as hematological malignancies.

While it is clear that aspirin therapy is associated with decreased risk for certain cancers and can inhibit metastasis, the underpinning mechanisms responsible for its multiple actions *in vivo* are not elucidated. Hawley *et al.* have shown that salicylate, a breakdown product of aspirin, activates AMP kinase (76,77). This is done by way of salicylate inhibiting

threonine-172 dephosphorylation, which in turn increases AMP kinase ability to produce ATP (77). Alternatively, diabetes drugs such as the thiazolidinediones (TZDs), a class of PPAR γ ligands, can stimulate AMP kinase function and decrease Cox-2 expression (78,79). TZDs and other PPAR γ ligands, have anti-proliferative and pro-apoptotic properties on hematological malignancies including multiple myeloma, Burtkit's lymphoma and myeloid leukemia cells (80–82). Whether aspirin and AMP kinase signaling are involved in the regulation of hematological malignancies has not yet been explored.

Interestingly, not all studies regarding aspirin have been promising. A study done by Cook *et al.* surveyed 39,876 women who were given aspirin (100 mg/every other day) or placebo. Cook's analysis showed a decreased risk for lung cancer (22%), but not for colorectal cancer, breast cancer or cancer of any other site (83). However, the dose and frequency (100 mg/every other day) of aspirin used in their studies is different from many of the previous studies. This raises important issues regarding dosing and timing of aspirin use when treating different types of cancer.

Furthermore, aspirin's beneficial properties come with unwanted side effects, the most common being gastrointestinal complications (84). Most of aspirin's adverse effects are associated with the inhibition of Cox-1, which disrupts prostanoid homeostasis in the gut. Pepper *et al.* showed that the aspirin analogs 2-hydroxy benzoate zinc (2HBZ) and 4-hydroxy benzoate zinc (4HBZ) can induce apoptosis in primary CLL cells by activating the caspase-3 signaling pathway. Of particular interest, 2HBZ and 4HBZ decrease Cox-2 expression, but do not affect Cox-1 levels. (85). Novel aspirin analogues could be used to selectively acetylate and inhibit Cox-2, thus minimizing Cox-1-related adverse effects. However, using aspirin as a preventive therapy against malignancies requires long-term use, thus it is important to carefully examine the risk to benefit profile for each individual. On going long-term studies, such as the ASPREE study (NCT01038583), will provide further information regarding the safety of long-term low-dose aspirin treatments (86).

Lipoxins and aspirin-triggered lipoxins: Novel therapeutic agents

The beneficial effects of aspirin, by which it decreases inflammation and prevents cancer, go beyond the inhibition of PGs and TXs production. Serhan *et al.* proposed that the aspirin-mediated Cox-2 acetylation is responsible for the production of the novel SPM namely, aspirin-triggered lipoxins and aspirin-triggered resolvins (87–89). Specialized proresolving mediators play a crucial role in the regulation of inflammation, particularly during the resolution phase. SPM resolve inflammation, restore tissue homeostasis and prevent chronic inflammation (19). Aspirin inhibits proinflammatory mediator production and in parallel induces the synthesis of pro-resolution SPM molecules. This unique mechanism may explain some of aspirin's beneficial effects during cancer treatment that are not observed with other NSAIDs.

Both arachidonic acid and docosahexaenoic acid (DHA) are precursors to different families of bioactive lipid mediators including SPM. Arachidonic acid and DHA, are omega-6 and omega-3 poly-unsaturated fatty acids (PUFA) respectively (19). PUFA have been shown to have protective effects on breast cancer, neuroblastoma and renal cancer development (90–

94). In breast cancer for example, PUFA increased the cytotoxic effects of doxorubicin and docetaxel on malignant cells while protectin healthy cells (90,91). In addition, Comba *et al.* showed in a mouse model that an omega-6 rich diet, which increases the levels of arachidonic acid in the cell membrane, decreased mammary gland tumor metastasis and volume, and consequently increased the animal's survival (95). Interesting observations tying together SPM and cancer have recently been made by Jin and colleagues, who showed that aspirin-triggered lipoxin A₄ has anti-angiogenic properties, as it significantly reduces VEGF-A-induced vascular angiogenesis *in vivo* (96). In addition, Chen *et al.* have recently described similar observations, in which lipoxin A₄ and its analog BML-111, decrease the production of the hypoxia-inducible factor (HIF)-1 α and VEGF in hepatocarcinoma cells. Likewise, in a murine model of liver cancer, lipoxin A₄ and BML-111 have been shown to regulate and inhibit hepatocarcinoma tumor growth (97,98). *In vitro* lipoxin A₄ also decreases AML cell migration, while promoting macrophage phagocytosis of apoptotic cells (99).

SPM are a relatively newly discovered family of bioactive lipids. Investigating the alternative biosynthetic pathways of Cox-2 as a way to decrease PGs and TXs production and increase the levels of beneficial SPM is a promising new area of study. Targeting SPM as well as SPM-promoting Cox-2 inhibitors could lead to development of highly effective and safer therapies for hematological malignancies and other cancers.

Concluding remarks

Current chemotherapeutic therapies against hematological malignancies are insufficient. Many patients develop resistance to treatment or suffer devastating relapse. Therefore, the development of new approaches to treat cancer is imperative. Given that Cox-2 plays a crucial role in cancer development, pursuing the use of Cox-2 inhibitors as preventive therapeutic agents holds great promise. The use of FDA approved Cox inhibitors could provide a distinct advantage, as it would expedite clinical studies and minimize the risk of unknown drug-related side effects associated with newly developed molecules.

There is burgeoning evidence regarding the applicability of NSAIDs, such as aspirin and other Cox-2 specific inhibitors, to treat hematological malignancies. Combining current therapeutic treatments, including radiation and chemotherapy, with Cox-2 inhibitors is a viable approach, which so far has provided promising results. Nonetheless, using Cox inhibitors to treat malignancies can still present unwanted health risks, and a better understanding of the mechanisms by which Cox inhibitors regulate inflammation and minimize the risk of cancer is essential in order to improve current treatments. Lastly, SPM have great potential to be used as anti-cancer agents. Novel therapeutic drugs, should aim to not only the inhibit Cox-2-mediated PGs and TXs production, but also to increase the production of SPM.

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Figure 1.

Cox-2 inhibitors can decrease the risk of cancer. Both non-aspirin NSAIDs and aspirin inhibit the ability of Cox-2 to produce proinflammatory prostaglandins (PGs) and thromboxanes (TXs). In addition, aspirin-mediated acetylation of Cox-2 (Ac-Cox-2) triggers the production of aspirin-triggered specialized proresolving mediators (AT-SPM), which have anti-cancer properties.