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Review

NSAID's - Potential Chemoprotective Agents against Cancer

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Abstract: Non steroidal anti-inflammatory drugs act by inhibiting cyclooxygenase enzyme in the plasma membrane predominantly. Now a day's many researchers has been observed a great involvement of these anti-inflammatory drugs in the cure of different types of cancers. So this review shows the role of cyclooxygenase inhibitors specifically type-2 in cure or prevention of different type of cancers.

Introduction

Internationally there are >10 million new cancer cases and >7 million cancer related death reported each year making cancer research a top priority. As per GLOBOCAN estimates approximately 12.7 million cancer cases and 7.6 million cancer deaths have been found to be occurring in 2008 worldwide. It is also observed that more than half of the cancer patients are found in developing countries [1, 2]. Cancer is a disease of cells characterized by reduction or loss of effectiveness in normal cellular control mechanism which regulates multiplication. Carcinogenesis is a multistep process as was first described in 1965 by Leslie Foulds, who deduced that there were multiple pathological processes of cancer induction and tumor progression for many human epithelial cancers.Carcinogenesis can be thought of as three stage process. The first stage is initiation which involves in the mutation by physical, chemical or viral exposure and occurs rapidly and a high frequency. The second stage is tumor promotion, a low frequency event that requires sustained chronic exposure to tumor promoters such as growth factors, hormones or ultraviolet radiation. The third stage is tumor progression in which tumor becomes malignant. Many cancer cells have defects in their progression through the cell cycle or their regulation of cell death. In particular, distinct feature of tumors is a lack of regulation of the cell cycle, resulting in uncontrolled proliferation. Although the goal of cell division is for each daughter cell

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to inherit one and only copy of each intact chromosome, defects in this process can lead to aneuploidy, genetic instability and ultimately, metastatic tumorigenesis.

In past, due to poor therapeutic response and high incidence of adverse reactions, chemotherapy was considered as a last resort, after more successful treatments like surgery and radiotherapy had failed. However, even with recent advances, the treatment of cancer continues to be one of the greatest challenges in medicine, as many forms of human cancers still resist effective chemotherapy. A major limitation in cancer therapy is in adequate selectivity of most anti cancer drugs [3].Some alternative strategies such as chemoprevention is also being investigated. Proof of concept of chemoprevention has been shown with the non-steroidal anti-inflammatory drugs (NSAIDs) [4]

Inflammatory conditions that predispose to cancer

Wide arrays of chronic inflammatory conditions predispose susceptible cells to neoplastic transformation. Most of the resulting tumors are of epithelial cell origin (carcinomas). The most widely studied and best established of these links are colon carcinoma associated with inflammatory bowel disease (chronic ulcerative colitis and Crohn's disease), esophageal adenocarcinoma associated with reflux esophagitis (Barrett's esophagus), hepatitis predisposing to liver cancer, schistosomiasis causing an increased risk of bladder and colon carcinomas, and chronic *Helicobacter pylori (H.pyroli)* infection leading to cancer of the stomach. Some increase in the incidence of lymphoma is also seen, particularly mucosal associated lymphoid tissue (MALT) lymphoma.

Chronic inflammatory model lead to progression of tumors

Animal models demonstrate experimentally that chronic inflammation predisposes to the development of various forms of cancer [5, 6]. For example, marmosets have a high incidence of spontaneous colitis and a high incidence of colon cancer as well [7, 8]. Skin cancer is induced by administration of carcinogens such as dimethylbenzanthracine (DMBA) followed by repeated administration of tumor promoters such as phorbol myristate acetate (PMA) orbenzoyl peroxide, which induces inflammation and the production of various inflammatory mediators [9]. Intraperitoneal introduction of mineral oils (*e.g.* pristane) or plastic discs into BALB/c mice promotes the formation of chronic granulomatous tissue and the development of plasmacytomas [10]. In these animal models, the tumors generally arise in the inflammatory tissue, indicating that local inflammatory mediators are responsible for their development. In some cases, there is strong evidence suggesting a genetic basis for the susceptibility to tumor development. For example, in the mouse plasmacytoma model, BALB/c mice are uniquely susceptible to developing plasma cell tumors in response to pristane, whereas most other strains are not. Similarly, SENCAR mice are uniquely susceptible to developing skin tumors in response to DMBA and PMA. These findings provide a basis for identifying critical genes and factors that contribute to tumor development and may explain why, for example, some individuals with chronic inflammatory conditions and carcinogen exposure (*e.g.* smokers) develop cancer while others do not. The types of chronic inflammation that lead to cancer are varied. In some cases, the progenitors of the inflammation are known. These include chronic bacterial and parasitic infections, chemical irritants and non digestible particles. In other cases, the

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underlying cause of the chronic inflammation is unknown. This is true for inflammatory bowel disease, sialadenitis and lichen sclerosis. Some of the known chronic inflammatory agents will be described below. Of these, parasitic infections are perhaps the best described. It seems that any parasitic infection that persists or recurs over many years can predispose to cancer. Thus, bacterial, viral and parasitic infections can all lead to cancer.

Progenitors of inflammation due to bacterial infections lead to cancer

The strongest association between chronic bacterial infection and the development of cancer involves the organism *H pylori* which is associated with at least a two fold-increased risk of adenocarcinoma of the stomach [11, 12]. In addition, *H pylori* infection is thought to increase the incidence of MALT lymphoma [13]. Strong experimental evidence that *H pylori* infection is carcinogenic comes from studies showing that gerbils infected with *H pylori* develop active chronic gastritis followed by induction of aberrant DNA methylation [14]. *H pylori* infection in humans is always accompanied by mucosal inflammation (gastritis) with an influx of lymphocytes, plasma cells, and neutrophils. The robust immune response to *H pylori* generally fails to clear the infection, thus resulting in a chronic inflammatory response thought to be a key element of the carcinogenic activity of the bacterium. Unless treated, *H pylori* infection and the associated gastritis persist for decades. Eradication of *H pylori* infection with antibiotics may also eliminate the excess risk for cancer, but this has not yet been established.

Progenitors of inflammation due to parasitic infections lead to cancer

Several parasitic infections are known to increase the risk of cancer. Schistosomiasis is prevalent primarily in third world countries and is difficult to treat because contaminated water supplies lead to re infection [15]. Chronic schistosomiasis induces cystitis, fibrosis and increases the incidence of carcinoma of the bladder, liver and rectum, and follicular lymphoma of the spleen, with different strains of the parasites infecting specific organs and leading to the various cancers [16]. Liver flukes (*Opisthorchis* and *Clonarchis*), introduced by eating raw fish, infect the bile duct and lead to chronic cholangitis associated with an increased incidence of cholangiocarcinoma [17]. Chronic infection and inflammatory diseases may also contribute to the development of Hodgkin's disease and non-Hodgkin's lymphoma [18].

Progenitors of inflammation due to viral infections lead to cancer

Many different viruses cause an increased incidence of cancer. Those most commonly associated with chronic inflammation are the hepatitis B and C viruses, which lead to chronic active hepatitis and hepatocellular carcinoma [19]. Epstein-Barr virus (EBV) is associated with B-cell non-Hodgkin's lymphoma, and may contain a chronic inflammatory component [20]. Other viral infections can also increase the incidence of cancer, but the role of inflammatory mediators is less clear. For example, the human papilloma virus, herpes simplex virus 2, and cytomegalovirus have been implicated in cervical and other carcinomas [21]. Among RNA retroviruses, the human immunodeficiency virus (HIV) predisposes to the development of non-Hodgkin's lymphoma, squamous cell carcinomas, and Kaposi's sarcoma while the human T-cell lymphoma virus causes adult T-cell leukemia [22]. Unlike the other parasitic

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infections described here, viruses implicated in inducing neoplasia directly infect the cells that ultimately undergo neoplastic transformation. Hence, it is difficult to determine whether these agents act by causing a chronic inflammatory condition, by directly transforming the cells that they infect, or both. Most of these viruses induce chronic increased proliferation of the infected cells, thus predisposing to neoplastic transformation. For example, EBV causes sustained proliferation of peripheral B-lymphocytes, but when coupled with a secondary mutation can result in malignant transformation, such as occurs with the chromosomal translocations that activate the *c-myc* oncogenes in Burkett's lymphoma. The hepatitis viruses are thought to give rise to hepatocellular carcinoma by causing liver damage and regeneration together with the generation of secondary inflammatory mediators [23].

Non-infectious causes of chronic inflammation lead to cancer

Various non-infectious agents also cause chronic inflammation associated with an increased risk of cancer. For example, esophageal reflux causes chronic exposure of the esophageal epidermis to irritation by gastric acids. This leads to reflux esophagitis, or Barrett's esophagus, and subsequent development of esophageal carcinoma [24]. Excess fecal bile acids in patients with primary sclerosing cholangitis and ulcerative colitis are associated with an increased risk of colorectal carcinoma. A recent publication demonstrated that ursodiol, a drug that reduces the colonic levels of deoxycholate and other bile acids (used to treat cholangitis), significantly reduces the incidence of neoplasia [25]. Chronic irritation of the liver by alcohol causes cirrhosis and hepatocellular carcinoma [26].

Non-digestible agents such as asbestos, coal and silica dust lead to chronic inflammation in the lung because of the inability of the immune system to remove the substances. Such sterile inflammations increase the incidence of epithelial cancers including mesothelioma and lung carcinoma [27]. Experimental evidence that chronic sterile inflammation can cause cancer comes from studies in BALB/c mice that received *i.p.* administration of non-digestible, non-genotoxic mineral oils or plastic disks. The mice developed a high incidence of B lymphocytic (plasma cell) tumors but no epithelial cancers [28].

Cigarette smoke is a complex pro-neoplastic agent that may act, in part, by inducing a chronic inflammatory condition. Smoking not only causes chronic bronchitis, but also delivers an array of genotoxic carcinogens (e.g. nitrosamines, peroxides) into the lungs. Hence, at present, it is unclear to what degree chronic bronchitis, mutagens in the smoke, and other factors contribute to the high incidence of lung carcinoma among smokers. There are limitations, however, to using epidemiology to understand the causes of cancer. Definitive evidence that chronic inflammation predisposes to cancer requires identification of the causative inflammatory mediators as well as the agents that prevent neoplastic transformation through inhibition of the inflammatory process. The reminder of this review will focus on the mechanisms whereby inflammatory mediators promote neoplastic transformation.

Prostaglandins a mediator responsible to development of cancer

Evidence from human and animal studies suggests that prostaglandins contribute to the development of cancer and targeting the prostaglandin (PG) pathway is potentially a critical intervention for the prevention and

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treatment of cancer [29, 30, 31]. Prostaglandins such as prostaglandin E2 (PGE2) are lipid mediators of the inflammatory immune response and are derived from oxidative metabolism of arachidonic acid. These lipids are synthesized in large quantities by inflammatory cells in response to both acute and chronic inflammatory stimuli. Two different cyclooxygenase (COX) enzymes catalyze the rate-limiting first step in prostaglandin synthesis [32]. COX-2 is expressed during inflammation. Its primary site of synthesis is inflammatory monocytes and macrophages, but it is also expressed in non inflammatory cells such as fibroblasts, epithelial cells, and endothelial cells. Bacterial cell products and inflammatory cytokines induce *in vitro* expression of COX-2. Notably, prostaglandin synthesis can also be stimulated by peroxynitrite, thereby providing for synergy between these two procarcinogenic inflammatory mediators [33]. Experimental induction of COX-2 in animal models is accomplished with agents that induce chronic inflammation such as administration of azoxymethane to rats. COX-1 is a constitutive enzyme expressed in most cell types and is associated with regulation of housekeeping functions such as gastric acid secretion.

Tumorigenesis promotes by prostaglandins

Many different mechanisms have been proposed to explain the mechanisms of tumorigenesis by prostaglandins. Prostaglandins can stimulate cell proliferation, induces synthesis of cytokines such as IL-6 that serve as tumor growth factors, synthesis of prostaglandins is coupled with formation of DNA-reactive by-products with mutagenic potential; e.g. formation of malondialdehyde (MDA) from prostaglandin G_2, and it also can induce angiogenesis, which is required for growth and metastasis of tumors. Some evidence of this comes from the demonstration that NSAIDs inhibit angiogenesis *in vitro*. It has been suggested that these drugs may not be acting entirely through the inhibition of PGE_2 synthesis because the addition of exogenous PGE_2 fails to overcome the inhibitory effect of the NSAIDs [34]. However, the concentrations of NSAIDs required to inhibit prostaglandin-independent angiogenesis *in-vitro* are quite high (*e.g.* 250 to 500 μM of indomethacin) and are unlikely to be achieved *in-vivo*. In contrast, inhibition of prostaglandin synthesis by NSAIDs occurs at concentrations that are achieved *in vivo* (*e.g.* 1 μM or less for indomethacin) [35]. In addition to serving as pro-inflammatory mediators, prostaglandins are also immunosuppressive. By inhibiting the functions of T cells and macrophages, they may decrease immune surveillance and thereby allow nascent tumor cells to escape detection by the immune system. Prostaglandins may inhibit apoptosis of tumor cells by increasing expression of the anti-apoptotic oncogenes *bcl-2* or by removing arachidonic acid, which is thought to be pro-apoptotic. It also stimulates cell signaling through peroxisome proliferator activated receptor delta (*PPAR-δ)*, a transcription factor that regulates proliferation-associated genes.

Cytokines

Inflammatory cells secrete a large number of cytokines and chemokines that can promote the outgrowth of neoplastic cells. These factors are produced in response to proinflammatory stimuli such as bacterial lipopolysaccharide. Neoplastic cells have a reduced need for normal metabolic factors, but they often require the presence of specific cytokines in order to proliferate, at

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least in the early stages of tumor development. Many tumor cells developing in chronically inflamed tissue cultivate a growth advantage by acquiring the ability to proliferate in response to cytokines. They may express growth factor receptors abnormally or alter their response to the factors by undergoing cell division instead of differentiation. Examples of tumor cell cytokine dependence in human disease are the growth dependence of AIDS- and EBV-associated B-cell lymphomas, B-cell leukemia, and multiple myeloma on the inflammatory cytokines IL-6 and IL-15 and the dependence of malignant mesothelioma on platelet-derived growth factor [36]. Monocytes, macrophages, and T cells are major sources of cytokines that promote outgrowth of preneoplastic and malignant cells, in addition to autocrine growth factor production by the tumor cells themselves.

Tumor progression mechanisms

Cytokines can contribute to tumor progression by mechanisms other than direct stimulation of cell growth. One such mechanism involves inducing the production of reactive oxygen and nitrogen intermediates. For example, TNF-alpha is known to enhance the formation of reactive oxygen intermediates by neutrophils and other cells. IL-1-beta, TNF-alpha, and interferon (IFN)-gamma stimulate expression of inducible nitric oxide synthases and the formation of nitric oxide in cholangiocarcinoma. This process has been shown to cause DNA damage and inhibit DNA repair in tumor cells. IL- 8 can promote tumorigenesis through two different mechanisms. One involves induction of angiogenesis, possibly through the synthesis of matrix metalloproteinase. In addition, IL-8 recruits inflammatory neutrophils to the site of inflammation and may be thereby increase formation of reactive oxygen and nitrogen intermediates. Some cytokines may also promote tumorigenesis by inducing immunosuppression, as is suggested for transforming growth factor-beta.

NSAIDs and novel agents

Chronic intake of NSAIDs may reduce carcinogenesis by inhibiting production of prostaglandins, cytokines, and angiogenic factors. Note that NSAIDs do not eliminate inflammation but rather act by reducing the production of selected inflammatory factors. Hence, unlike steroids, they do not suppress elements of the immune response that are necessary for tumor depletion such as T cells, NK cells, and macrophages. COX-2 selective inhibitors may provide a safer method for chemoprevention than older NSAIDs such as aspirin and indomethacin, which also inhibit COX-1 activity and cause gastric lesions. NSAIDs exert analgesic, antipyretic, and anti-inflammatory effects through the inhibition of COX-catalyzed biosynthesis of prostaglandin’s [37]. Moreover, the ability of these NSAID’s drugs to prevent cancer is thought to be due, in part, to COX inhibition. Currently, there are two known isoforms of COX, both of which catalyze the metabolism of arachidonic acid to prostaglandin H_2, a precursor to prostaglandins [38]. The COX-1 isoform is constitutively expressed and produces the prostaglandins important for normal physiological function. COX-2 can be induced by cytokines, growth factors, and tumor promoters and produces prostaglandins at sites of inflammation [39]. In carcinogenesis, over expression of COX is thought to deregulate arachidonic acid metabolism and lead to elevated prostaglandin production [40]. Increased prostaglandin levels have been observed in human and animal tumors compared with surrounding normal tissue and are thought to contribute to colon carcinogenesis by

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influencing cell proliferation, tumor promotion, immune response, and metastasis [41, 42].

The role of arachidonic acid metabolites as modulators in the multi-step process of carcinogenesis, particularly in tumor promotion, has often been postulated with supportive evidence from epidemiological and experimental studies. This notion is strengthened by reports on a reduced mortality and a lower incidence of human colon cancer following chronic consumption of NSAIDs, *e.g.* acetylsalicylic acid [43]. Sulindac and indomethacin suppress the number and size of colonic polyps in patients with familial adenomatouspolyposis [44, 45]. In accord with the human data, animal studies have shown an anti-carcinogenic action of NSAIDs on gastrointestinal and other tumors. Moreover, inhibitors of cyclooxygenase and lipoxygenase activities decrease the tumor promoting effects of various structurally unrelated agents and inhibit the growth of tumor cells *in vivo* and *in vitro*. The impact of arachidonic metabolism on tumorigenesis is further strongly suggested by the following observations: (i) the levels of specific metabolites of arachidonic acid and the expression of cyclooxygenase and lipoxygenase are enhanced in various human and rodent tumors (ii) the cyclooxygenase isoenzyme COX-2 is induced in normal tissues by the treatment with tumor promoters, *e.g.* TCDD and TPA [46]. Interestingly, the induction of COX-2 has been observed in pathological processes including tumor promotion. Thus, in a quest for a more mechanistic risk assessment pertaining to tumor promoters such as dioxin-like compounds, the expression of cyclooxygenase activities may provide an important link necessary for this goal [47].

Chemo-protection by NSAIDS: as evidence

A growing body of evidence suggests that anti-inflammatory medications, such as aspirin, NSAIDs and more recently COX-2 selective inhibitors, have a chemoprotective effect against a variety of neoplasms [48]. There is compelling epidemiological evidence that the regular or occasional use of aspirin or other NSAIDs drug is inversely related to the risk of cancer [49, 50]. The reduction in relative risk varies between 50% and 90%. A large study conducted by the American Cancer Society reported a 40% reduction in risk of cancer in individuals who used aspirin 16 or more time per month compared with those who never used aspirin. In addition a population based case-control study found that current users of aspirin and other NSAIDs has an almost 50% reduction in the risk of developing either adenocarcinoma or squamous cell carcinoma. Beside the epidemiological evidence, experimental and preclinical evidence suggest a possible preventive or therapeutic benefit of aspirin or other NSAIDs in cancer. For example, Li *et al.* reported that treatment with aspirin resulted in significant growth inhibition of 10 esophageal cancer cell lines [51]. This growth inhibition was time and dose dependent and was associated with induction with apoptosis. Also, Rubio previously showed that the indomethacin suppressed the development and growth of chemically induced esophageal cancer in mice either when given in tandem with NMBA (a potent esophageal carcinogen) or when its delivery was delayed to allow tumor development [52, 53]. Taken together, the evidence suggests a potential role for aspirin and other NSAIDs in the prevention, and possible treatment, of esophageal cancer. The only well known function of NSAIDs to date is their ability to suppress prostaglandins synthesis.

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COX-2 contributes to cancer: as preclinical evidence

Evidence suggests that COX-2 may contribute to esophageal carcinogenesis. Increased amount of COX-2 are commonly found in adenocarcinoma as well as squamous cell carcinoma of the esophagus [54]. In addition, over expression of COX-2 has been observed in premalignant condition of the esophagus, such as squamous dysplasia and Barrett's esophagus [55]. Shirvani *et al.* reported a progressive increase in COX-2 expression with increasing histological severity from metaplasia to low-grade and high-grade dysplasia [56]. Increased COX-2 expression has also been associated with decreased survival in patient with esophageal adenocarcinoma. However, the most direct evidence supporting a cause-and-effect connection between COX-2 over expression and carcinogenesis comes from genetic studies. In a seminal study Oshima *et al.* reported that knocking out the COX-2 gene significantly reduced the numbers of intestinal polyps in a mouse model of familial adenomatous polyposis. In another study, forced expression of the COX-2 gene in the mammary gland of transgenic mice led to the development of mammary cancer [57]. These studies provide the most direct evidence of a cause and effect relationship between COX-2 and cancer development.

Reactions catalyzes by COX ***[Fig. 1]***

a. Insertion of molecular oxygen into arachidonic acid

b. Conversion to PGH_2 by the peroxidase activity [58].

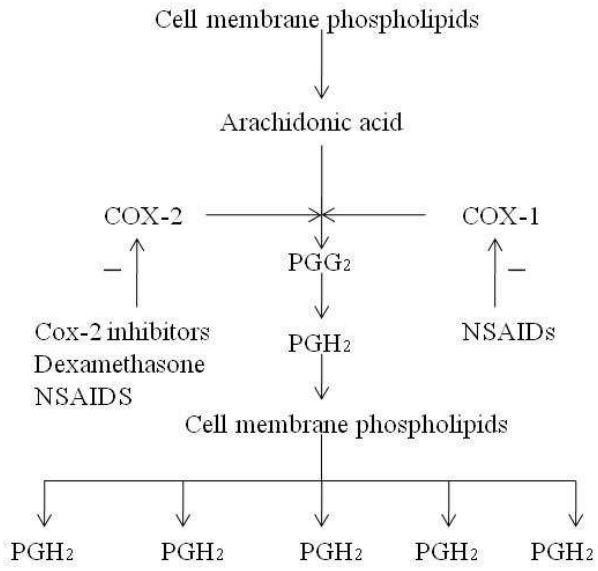

Figure 1 Biosynthetic pathway for eicosanoid derived from arachidonic acid.

Possible mechanism of COX-2 induced carcinogenesis

The effects of COX-2 is attributed by several pathways that are potentially involved in the initiation and progression of cancer, including xenobiotics metabolism, apoptosis, angiogenesis, inflammation, and immune surveillance.

Modification of known indomethacin to improve its specificity for COX-2

The Merck Frosst first reported improving the selectivity of indomethacin for COX-2 by making the larger trichlorobenzoyl analogue **[Fig. 2].**

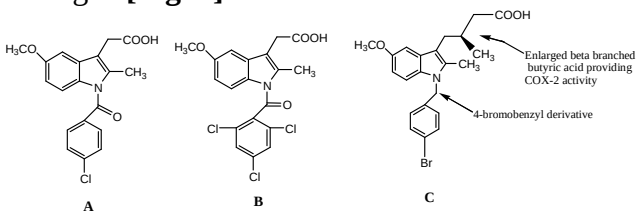

Figure 2 Modification of known Indomethacin molecule (A) Indomethacin

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(B) Trichlorobenzoyl analogue (C) Enlarged *B* branched and 4-bromobenzyl derivatives

Exchanging the carboxylic acid moiety of indomethacin for a 4-bromophenyle thiazole group **[Fig. 3]** afforded the highly selective COX-2 inhibitor.

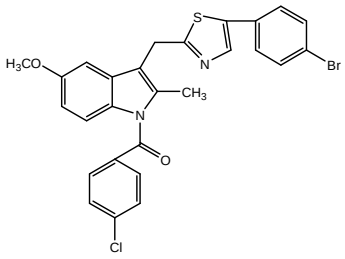

Figure 3

It is not known how the 1-benzoylindole **[Fig. 4],** lacking a side chain at C-3 of the indole nucleus , bind to the active site in COX-2 , but in a cell based assay inhibited prostaglandin formation by COX-2 [58].

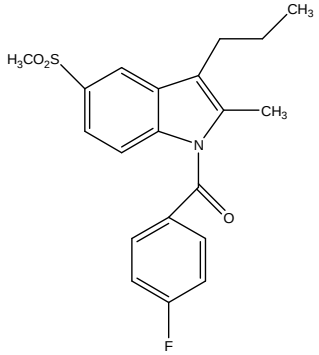

Figure 4

Future direction

The substantial body of experimental and preclinical work reviews shows that a link exists between COX-2 and tumor development or progression. However, the role of COX-2 inhibitor in the prevention or treatment of human tumors remains unsubstantiated. Numerous studies are currently in progress to evaluate both the safety and efficacy of COX-2 inhibitor given either as chemo preventive agent in patients at high risk for tumor development or in combination with standard cytotoxic agent to treat existing malignancies. The present study may lead to discovery of new or better anti cancer agents [60].

Conclusion

This review will summarize the clinical association between chronic inflammation and cancer and will describe the inflammatory factors and pathways that are thought to be pro-neoplastic agents. Emphasis will be placed on examining the role of the reactive oxygen species, nitrogen intermediates, cytokines and prostaglandins. It also indicates that addition of NSAIDs to conventional anti-cancer therapies may enhance their antitumor effect.

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