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Review article

CASUAL RELATIONSHIP BETWEEN PROGRESSION OF CANCER AND PRESCRIBED NSAIDS-COMPREHENSIVE REVIEW

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ABSTRACT

This comprehensive exploration delves into the multifaceted relationship between Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and cancer, with a specific focus on colorectal cancer. The synthesis of extensive clinical data establishes NSAIDs as pivotal in cancer treatment, particularly in colorectal cancer prevention. The National Comprehensive Cancer Network's recognition of NSAIDs in the 2017 colorectal cancer guide signifies a milestone in integrating these drugs into clinical protocols. While long-term NSAID use exhibits anticancer effects, the associated side effects necessitate a nuanced consideration of risks and benefits for individual patients contemplating cancer chemoprophylaxis. The review encompasses the mechanisms underlying NSAID action, their impact on inflammatory pathways, angiogenesis, immune modulation, and their role in preventing cancer metastasis. The nuanced discussion highlights the need for future research, emphasizing molecular classifications, population-specific studies, and optimal NSAID dosage for maximizing anticancer benefits.

Key Words:- NSAIDs, Colorectal Carcinoma, COX, Mediators.

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INTRODUCTION

Recently research across diverse scientific fields, including toxicology, pharmacology, clinical medicine, and epidemiology, has been increasingly suggestive of the potential benefits of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) in mitigating the occurrence or progression of colorectal cancers, polyps, and potentially other gastrointestinal tumors (Rees, K., *et al*., 2011). The practical application of these findings for preventing such cancers in humans now requires serious consideration. Recent insights from various biological research areas propose that NSAIDs may reduce the risk of human large bowel cancer and potentially cancers at other gastrointestinal sites. Evidence supporting this notion has emerged from animal toxicology, experimental pharmacology, clinical medicine, and epidemiology (Xu, X. D., *et al.*, 2015). Both preclinical and clinical studies have distinctly highlighted the advantages of using NSAIDs to lower cancer risk. NSAIDs and coxibs function by inhibiting prostaglandin biosynthesis. Prostaglandin E2 (PGE2), among the prostaglandins produced at elevated levels in the tumor microenvironment, is believed to play a significant role in cancer progression. A plethora of experimental, epidemiologic, and clinical studies suggests that NSAIDs, especially highly selective cyclooxygenase (COX)-2 inhibitors, hold promise as antitumor agents (Garon, E. B., *et al*., 2015). NSAIDs contribute to restoring normal apoptosis in human adenomatous colorectal polyps and various cancer cell lines that have lost adenomatous polyposis coli gene function. Additionally, NSAIDs inhibit angiogenesis in cell culture and rodent models of angiogenesis. Numerous epidemiologic studies indicate that long-term NSAID use is associated with a reduced risk of colorectal cancer, adenomatous polyps, and, to some extent, a lower incidence of other cancers. Sulindac and Celecoxib, two NSAIDs, have demonstrated inhibitory effects on

adenomatous polyp growth and regression of existing polyps in randomized control trials involving patients with familial adenomatous polyposis (FAP).

INFLAMMATORY MEDIATORS

COX enzymes play a pivotal role in the synthesis of prostaglandins (PGs), which are lipid compounds derived from the arachidonic acid pathway. These COX-generated prostaglandins, categorized as eicosanoids, have widespread presence in the body and serve various physiological functions, acting as mediators of inflammation. The process of prostaglandin synthesis initiates with phospholipase A2 (PLA2) enzymatically acting on membrane phospholipids, yielding arachidonic acid (AA). COX then catalyzes the conversion of AA into prostaglandins through two successive steps: dioxygenase activity producing prostaglandin G2 (PGG2) and subsequent reduction of PGG2 to prostaglandin H2 (PGH2) via peroxidase activity. Tissue-specific synthases contribute to the synthesis of prostaglandin thromboxane A2 (TXA2) from PGH2. During inflammation, PGE2 enhances vasodilation and increases microvascular permeability, leading to characteristic signs of redness and swelling. Additionally, PGE2 acts on sensory nervous system nerve terminals, contributing to the pain experienced during inflammation. Conversely, PGI2 acts as a potent vasodilator and inhibitor of platelet aggregation (Rees *et al*., 2011).

Research indicates that PGD2, primarily produced by activated mast cells, plays a crucial role in initiating type I acute allergic responses mediated by immunoglobulin E (IgE). Another prostaglandin, PGF2, predominantly derived from COX-1 in the female reproductive system, is involved in ovulation, uterine contraction, and the initiation of parturition. Notably, PGF2_ has been identified at inflammatory sites, such as synovial fluid in joints affected by rheumatoid arthritis and other arthritic conditions. Platelets, once recognized primarily for their role in hemostasis, are increasingly acknowledged for their involvement in inflammation and cancer. TXA2, derived from PGH2 in activated platelets, exerts vasoconstrictor and platelet aggregation-stimulating effects. Beyond its hemostatic role, TXA2 has been implicated in inflammation, allergic reactions, modulation of acquired immunity, angiogenesis, and cancer cell metastasis. Furthermore, platelets contribute to tumor progression by promoting tumor cell survival, enhancing tumor cell adhesion to the endothelium, and producing lipid products like TXA2, which contribute to increased tumor vascularization and dissemination into the bloodstream. Research has indicated platelet-induced overexpression of COX-2 in human colon carcinoma cells, linking increased COX-2-dependent PGE2 synthesis to tumorigenesis and tumor immune evasion. Additionally, PGE2 has been associated with promoting colorectal cancer stem cell expansion and metastasis.

INFLAMMATION AND CANCER

Inflammation is a complex biological response that serves as the body's defense mechanism against harmful stimuli, such as pathogens, damaged cells, or irritants. While acute inflammation is a crucial part of the immune system's response to injuries and infections, chronic inflammation can lead to various health issues, including cancer. The relationship between inflammation and cancer has been extensively studied, and research suggests that chronic inflammation creates a microenvironment conducive to the development and progression of cancer (Bansal *et al*., 2018). Several key factors contribute to this connection:

Inflammatory Mediators:

Inflammation involves the release of various signaling molecules, such as cytokines, chemokines, and prostaglandins. These molecules play roles in cell signaling and immune response regulation. However, when inflammation becomes chronic, these mediators can contribute to genetic mutations, cellular damage, and an environment that supports cancer growth.

Immune System Dysfunction:

Chronic inflammation can compromise the immune system's ability to effectively eliminate abnormal cells. Prolonged exposure to inflammatory signals may lead to immune system dysfunction, allowing the survival and proliferation of cells with genetic alterations that could otherwise be targeted and destroyed.

DNA Damage:

Inflammatory responses can cause DNA damage in surrounding cells. This damage may lead to genetic mutations, which, if left unrepaired, can contribute to the development of cancer. The continuous cycle of tissue damage, repair, and inflammation creates an environment conducive to the survival and growth of cancerous cells.

Angiogenesis and Tissue Remodeling:

Inflammation is associated with processes like angiogenesis (the formation of new blood vessels) and tissue remodeling. While these processes are vital for normal wound healing, in chronic inflammation, they can provide essential nutrients to support tumor growth and create an environment that facilitates the invasion of cancer cells into surrounding tissues.

Inflammatory Diseases and Cancer Risk:

Certain chronic inflammatory conditions, such as inflammatory bowel disease (IBD), chronic hepatitis, and chronic pancreatitis, are known to increase the risk of developing specific types of cancer. The persistent inflammatory state in these conditions contributes to a higher likelihood of genetic mutations and tumor

formation. Understanding the intricate links between inflammation and cancer has led to the development of targeted therapies aimed at disrupting these pathways. Drugs that inhibit inflammatory mediators or modulate the immune response are being explored for their potential in cancer prevention and treatment. Additionally, lifestyle factors such as diet, exercise, and stress management play roles in modulating inflammation and may impact cancer risk.

COX and Cancer progression

The prostaglandins produced by COX-2 are implicated in tumor-associated angiogenesis, modulation of the immune system, regulation of cell migration and invasion, and the inhibition of apoptosis. These diverse effects collectively contribute to the advancement of cancer. Furthermore, the byproducts of the COX-2 pathway, including Malondialdehyde, have the capacity to directly form DNA adducts. This process can lead to mutations, serving as potential initiators of carcinogenesis. The culmination of these effects actively stimulates tumor progression, providing insights into the pro-neoplastic role played by COX-2. One notable prostaglandin produced in the gastrointestinal tumor microenvironment through the COX-2 pathway is PGE2. This underscores the significance of COX-2 and its associated products in influencing the complex processes that drive cancer development and progression (Suchroska *et al*., 2016).

Cancer in Chronic inflammatory cases

To gain a comprehensive understanding of the role of NSAIDs in cancer, it is crucial to explore the intricate connection between chronic inflammation and carcinogenesis. The idea linking chronic inflammation to cancer was initially proposed by Virchow over a century ago in 1863. His observations highlighted that sites experiencing chronic inflammation were primary loci for cancer initiation, and the tissue injury induced by certain irritants promoted cell proliferation. Shared molecular targets and signaling pathways in apoptosis, cell proliferation, and angiogenesis are central to both inflammation and carcinogenesis. The dysregulation of these pathways during chronic inflammation often results in the abnormal expression of pro-inflammatory genes, contributing to malignant transformation.

Several cytokines play a pivotal role in tumor development, acting as a double-edged sword depending on the tumor microenvironment. Certain cytokines, with antitumor effects, can induce cell transformation and malignancy in the context of chronic inflammation. Key cytokines involved in inflammation and the tumor microenvironment include tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), transforming growth factor-beta (TGF-β), and interleukin-10 (IL-10). The intricate link between cancer and chronic inflammation is further underscored by the expression of cytokines, chemokines, and their receptors by many cancer cells. These molecules play crucial roles in cell proliferation, angiogenesis, cell migration, and metastasis. Beyond cytokines, other pro-inflammatory molecules like inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) are upregulated during chronic inflammation. The widely accepted consensus is that chronic inflammation is intricately involved in the process of carcinogenesis. The underlying causes for cancer development due to inflammation can be attributed to both infectious and noninfectious factors (Suchroska *et al*., 2016).

NSAID AND CANCER

Types of NSAID's

NSAIDs, a diverse family of drugs available over-the-counter or by prescription, are commonly employed to address inflammation, pain, or fever. Their anti-inflammatory efficacy stems from inhibiting COX enzymes responsible for converting arachidonic acid into prostaglandinH2—a precursor for synthesizing eicosanoids, including prostaglandins (PG), prostacyclin, and thromboxane A2. The primary products of COX activity, namely PGE2, PGD2, and PGF2a, play roles in promoting inflammation, pain, and fever. The ground breaking work of Vane demonstrated that aspirin's anti-inflammatory effect arises from suppressing PG synthesis, with subsequent research attributing this effect to COX inhibition. Beyond their involvement in inflammation, eicosanoids are crucial for maintaining gastrointestinal mucosa homeostasis, regulating blood clotting, managing blood flow, and supporting kidney function. Two distinct COX isoforms, COX-1 and COX-2, have been identified. COX-1 is constitutively expressed in most tissues, while COX-2 is induced by inflammatory stimuli, mitogens, or growth factors and is typically associated with pathological processes. Traditional NSAIDs like aspirin, ibuprofen, sulindac, and indomethacin inhibit both COX-1 and COX-2, although aspirin employs a unique mechanism involving irreversible acetylation of a serine residue in the catalytic domain of both enzymes. Recognizing that COX-2 is the primary mediator of inflammation prompted the development of a new class of inhibitors with COX-2 selectivity, known as coxibs. This innovation aims to circumvent gastrointestinal and renal toxicities linked to nonselective NSAIDs.

Mechanisms of prevention of cancer/metastasis

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) play a crucial role in preventing metastasis in cancer, showcasing their potential not only as anti-inflammatory agents but also as valuable components in cancer management. Several studies and clinical trials

have investigated the impact of NSAIDs on the metastatic spread of cancer, providing valuable insights into their preventive capabilities (Rothwell *et al.*, 2012).

Inhibition of Inflammatory Pathways:

NSAIDs, including aspirin, ibuprofen, and others, function by inhibiting cyclooxygenase (COX) enzymes, particularly COX-2. These enzymes are involved in the synthesis of prostaglandins, which play a pivotal role in inflammation. Chronic inflammation has been linked to cancer progression and metastasis, and by targeting COX-2, NSAIDs mitigate this inflammatory response.

Reduced Angiogenesis:

Tumors require a blood supply for sustained growth, and angiogenesis (formation of new blood vessels) is a critical step in this process. NSAIDs, by suppressing COX-2, hinder the production of pro-angiogenic factors, thus impeding the tumor's ability to develop a robust blood vessel network. This limitation in angiogenesis can restrict the spread of cancer cells to distant sites.

Immune Modulation:

NSAIDs influence the immune system in ways that can impact cancer progression. They may enhance the body's immune response against cancer cells, contributing to the prevention of metastasis. Moreover, by modulating inflammatory mediators, NSAIDs can create an environment less conducive to the survival and spread of cancer cells.

Clinical Evidence:

Numerous epidemiological studies, as exemplified by Rothwell et al., have demonstrated the benefits of NSAIDs in preventing cancer metastasis. These studies, encompassing large cohorts and randomized clinical trials, consistently show a reduction in metastatic incidence and improved survival rates among patients using NSAIDs, particularly aspirin.

NSAIDs-Distant metastasis

There is dependant relationship between NSAIDs and cancer metastasis based on eleven studies involving a substantial cohort of 247,826 patients and more than 40,000 events. The focus was on exploring the risk estimates for cancer distant metastasis in patients exposed to NSAIDs either before or after diagnosis. In the comprehensive analysis, ten out of the eleven studies consistently reported a negative association between NSAIDs and cancer metastasis. Although the results from two studies did not reach statistical significance, the overall trend indicated a potential protective effect of NSAIDs. Intriguingly, one study stood out by revealing a positive relationship between NSAIDs and cancer metastasis, and this finding was statistically significant. When collectively assessing the data, cancer patients who took NSAIDs exhibited a significant reduction in the risk of developing metastasis compared to the reference group. This overall trend towards a lower risk of metastasis in NSAID-exposed patients aligns with the majority of the analyzed studies, reinforcing the potential impact of NSAIDs in mitigating cancer metastatic processes (Corley *et al*., 2003).

NSAIDs-Lymph Node Metastasis

Literature discusses an investigation into the relationship between NSAIDs and lymph node (LN) metastasis. This analysis involved six studies, encompassing 110,735 participants and approximately 20,000 patients with LN metastasis. The primary focus of these studies was on examining the connection between the pre-diagnostic use of NSAIDs and the occurrence of LN metastasis. It's noteworthy that the studies predominantly involved clinical trials related to breast cancer and prostate cancer. Within this analysis, four out of the six studies identified an association between the pre-diagnosis use of NSAIDs and a reduced risk of LN metastasis. However, only one of these studies reported statistically significant results. Despite the variations in statistical significance, the overall trend suggested a decrease in the risk of LN metastasis in individuals who used NSAIDs before diagnosis, compared to the referent group. This observation underscores the potential role of NSAIDs in mitigating the risk of lymph node metastasis, particularly in the context of breast and prostate cancer clinical trials (Garon *et al*., 2015).

NSAIDs as primary preventive therapy

Numerous extensive epidemiological studies have consistently demonstrated the substantial benefits of prolonged use of low-dose aspirin (ranging from 75 to 300 mg daily) in effectively inhibiting various cancer incidences, reducing malignant cancer metastasis rates, and significantly improving overall survival rates for patients. Specifically, the aspirin group exhibited a noteworthy decrease in the risk of esophageal cancer, gastric cancer, cholangiocarcinoma, and breast cancer. In a comprehensive analysis conducted by Rothwell et al, encompassing five large randomized clinical trials that investigated the impact of aspirin (administered at 75 mg daily or more) on tumors, compelling results were unveiled. The analysis revealed that aspirin could reduce the incidence of distant metastases by a substantial 36% and lower the risk of cancer-specific mortality by an impressive 50% when compared to the control group. Moreover, for patients with adenocarcinoma, the risk of morbidity saw a notable reduction of 46%. In those without metastatic adenocarcinoma at the initial diagnosis, the long-term use of aspirin during subsequent observation periods was associated with a remarkable

70% reduction in cancer metastasis rates. Furthermore, distinguishing characteristics of NSAIDs, including aspirin, were identified in their ability to induce tumor cell apoptosis, down-regulate EGFR expression, and provide protective and reparative effects against DNA damage. These multifaceted mechanisms contribute to the observed benefits of aspirin in cancer prevention and management, shedding light on its potential as a valuable therapeutic adjunct in the realm of oncology.

NSAIDs and Colorectal cancer

The relationship between Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and colorectal cancer has been a subject of extensive research, with numerous studies highlighting the potential preventive effects of these drugs on colorectal carcinogenesis (Huang et al., 2014). Colorectal cancer is a significant global health concern, and understanding how NSAIDs impact its development and progression is crucial for developing effective preventive strategies (Sekandarzad *et al.*, 2017).

1. Aspirin:

Numerous studies, including randomized controlled trials and meta-analyses, have demonstrated the potential of aspirin in preventing colorectal cancer. The long-term use of low-dose aspirin has been associated with a significant reduction in colorectal cancer incidence and mortality.

2. Ibuprofen:

Ibuprofen, a commonly used NSAID, has also been investigated for its potential in colorectal cancer prevention. Some studies suggest a protective effect, possibly through its anti-inflammatory and COX-inhibitory actions (Flossman *et al.*, 2007).

3. Celecoxib:

Celecoxib, a selective COX-2 inhibitor, has been studied for its role in colorectal cancer prevention. However, concerns about cardiovascular side effects have tempered its widespread use (Arber et al., 2006).

Considerations and Challenges:

Risk-Benefit Profile: While NSAIDs show promise in colorectal cancer prevention, their long-term use must be weighed against potential side effects, especially in terms of gastrointestinal and cardiovascular risks.

Individual Variation: Response to NSAIDs may vary among individuals, and factors such as genetic predisposition and overall health should be considered.

Timing and Dosage: The optimal timing, duration, and dosage of NSAID use for colorectal cancer prevention are areas of ongoing research.

CONCLUSION

The clinical data supporting the use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in cancer treatment has expanded significantly, with particular attention to colorectal cancer. The 2017 version of the National Comprehensive Cancer Network colorectal cancer guide acknowledges the role of NSAIDs in the secondary prevention of cancer, marking a milestone in integrating these drugs into clinical protocols. However, the long-term use of NSAIDs comes with potential side effects, necessitating a careful consideration of the risks and benefits for individual patients contemplating their use as cancer chemoprophylaxis.

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