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From Pain Relief to Cancer Defense: The Promise of NSAIDs

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

NSAIDs (Non-Steroidal Anti-inflammatory Drugs) are commonly used to treat various types of pain and inflammation. In recent decades, extensive scientific research has been conducted to examine the use of NSAIDs in the treatment and prevention of cancer. Chronic inflammation has been linked to various cancer types, suggesting that prolonged inflammation can promote genetic mutations and accelerate their accumulation within cells. The COX pathway, short for Cyclooxygenase pathway, is a critical biochemical pathway in the human body involved in the production of important signaling molecules called prostaglandins. Key factors like COX enzymes and cytokines are important in the development and progression of inflammation-induced cancer. Angiogenesis occurs during inflammation, and it plays a major role in cancer development and metastasis. NSAIDs inhibit this process, which may also contribute to their anticancer effects. This review highlights the potential of NSAIDs, particularly aspirin, ibuprofen, and celecoxib, to influence various aspects of tumor behavior. Although promising, further rigorous studies are needed to establish their clinical efficacy and safety in diverse cancer scenarios. The use of NSAIDs as adjunctive therapies along with conventional treatments presents a promising avenue for enhancing cancer management strategies.

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1. INTRODUCTION

Non-steroidal Anti-inflammatory Drugs (NSAIDs) are commonly used medications. They are used to treat pain, inflammation, and fever, and are used for a range of conditions from minor aches and pain to arthritis and cardiovascular disease. Despite their widespread use, NSAIDs are not without risks and may cause significant adverse effects, including gastrointestinal bleeding, renal-dysfunction, and cardiovascular events [1]. Over the course of recent decades, a considerable and expanding volume of scientific investigation has been dedicated to examining the potential utilization of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) in both the treatment and prevention of cancer. This new area of study is closely connected to our existing knowledge of how chronic inflammation is linked to cancer development. The association between prolonged inflammation and the onset of various types of cancer has been recognized for a significant duration, and this knowledge serves as a foundational basis for the exploration of NSAIDs as potential tools in the battle against cancer [2].

2. CANCER AND ITS RELATIONSHIP WITH INFLAMMATION

Several cancer types exhibit varying rates of diagnosis in the human population, and this occurrence is linked to age-related patterns, suggesting the involvement of four to seven critical, unpredictable events that limit the progression of these cancers. The specific order in which capabilities are acquired can exhibit significant variation, both within tumors of the same category and notably among tumors of diverse categories.

Numerous types of malignancies, including cancer, lung cancer, prostate cancer, and sarcoma, often manifest initially at the site of inflammation or infection. This observation suggests that persistent infection can potentially cause chronic inflammation, which, in turn, can increase the likelihood of genetic mutations and accelerate the rate at which mutations accumulate within cells [3-6].

Cyclooxygenase (COX) is an enzyme involved in the production of prostaglandins, which are lipid molecules associated with inflammation. COX inhibitors, such as aspirin and ibuprofen, are commonly used as analgesics and anti-inflammatory drugs. Some studies have suggested that COX inhibitors may have protective effects against certain types of cancer [7].

Cytokines are a group of proteins that play role in cell signaling and immune system regulation. Some cytokines have been found to be involved in the development and progression of cancer. For example, tumor necrosis factor (TNF) is a cytokine that can promote tumor growth and survival, whereas interferons are cytokines that can have anti-tumor effects.

Inflammation can contribute to angiogenesis, and therefore, may play a role in cancer development. Additionally, chronic inflammation has been linked to an increased risk of certain types of cancers [7].

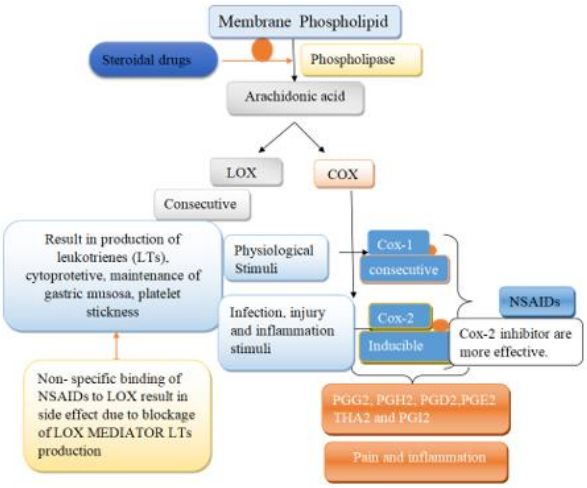

Fig. 1. Cancer and its Relationship with Inflammation

3. INFLAMMATION AND TUMOR MICROENVIRONMENT

Inflammation-driven responses produce specific chemical factors and cytokines that promote tumor progression. These factors operate through paracrine and autocrine mechanisms, actively attracting inflammatory cells to the tumor microenvironment. This process enhances the involvement of inflammatory cells in the tumor microenvironment [8].

When activated, inflammatory cells can release oxides that may induce DNA damage in proliferating cells, thereby generating reactive oxygen and nitrogen species [9]. Mutations brought about by inflammation can lead to the inactivation and inhibition of the dislocation repair genes, and dislocation repair enzymes can be directly oxidized to inactivate ROS [10].

From a mechanistic viewpoint, numerous inflammatory cells linked with neoplasms contribute to the increased discharge and accumulation of various inflammatory substances within malignant regions. These substances initiate the signaling pathways STAT3, NF-B, PI3K/Akt, and p38 MAPK, which are closely related to tumor signaling. These pathways subsequently play a pivotal role in coordinating the recruitment of inflammatory cells and secretion of factors that promote a pro-inflammatory milieu [11].

The tumor microenvironment (TME) is the internal environment in which tumor cells proliferate and live, and it includes tumor cells and various fibroblasts and neighboring cells. Immune, cancer and stromal cells form a complex regulatory network in the TME [12].

Epithelial and immune stem cells, which bear driver mutations or are in the early stages of cancer development, play a pivotal role in the initiation of aberrant pathway signaling that hinder the process of cell death and lead to uncontrolled cell proliferation, thereby inducing tissue stress that promotes a chronic inflammatory microenvironment. Oncogenes with gene-driver mutations, including Kirsten rat sarcoma (K-RAS), rearranged during transfection (RET), or MYC, have the ability to continuously activate pathways that enhance the expression and secretion of various proinflammatory cytokines, such as IL-1b, CSFs, IL-8, and CXC chemokines [13-15].

Immunostimulation and immunosuppression often occur in cancer and various cytokines such as macrophage migration inhibitory factor, TNF-α, IL-6, IL-10, IL-18 and TGF- β upregulate inflammation into cancer [16,17,18].

Pro-inflammatory cytokines are crucial controllers of the tumor microenvironment, governing the proliferation of cancerous cells, stimulating inflammation, and facilitating the metastasis of tumors [19].

4. TUMOR ANGIOGENESIS AND ITS RELATIONSHIP WITH INFLAMMATION

Angiogenesis is a fundamental natural or pathological phenomenon that is distinguished by the emergence of blood vessels from the current vasculature. The formation of new blood vessels is crucial for numerous normal physiological activities, including fetal growth and the healing of wounds. However, pathological angiogenesis is a critical hallmark of solid tumors, and it is the rate limiting step in the progression of tumors. In addition, repair enzymes play a vital role in the regulation of angiogenesis, controlling the balance between normal and aberrant blood vessel growth [20].

The interrelation between inflammation, angiogenesis, and cancer is widely acknowledged in contemporary biomedical research. Global estimates suggest that approximately 16% of cancer cases are attributable to infections, underscoring the significance of immunologic mechanisms in carcinogenesis. Moreover, nearly a quarter of all inflammatory responses are anticipated to culminate in tumorigenesis, emphasizing the intricate connections between inflammation, angiogenesis, and cancer. These findings underscore the need for continued exploration of the complex interactions between these critical biologic processes to identify novel targets for cancer prevention and treatment. [21].

During the inflammatory process, the hyperpermeability of the endothelium is facilitated by cytokines and chemokines via two transport mechanisms which aid in the recruitment of immune cells to the affected region [22,23]. In this process,

Vesiculo - vacuolar organelles (VVOs) that are dependent on caveolin form trans endothelial channels in specific regions of the plasma membrane. This sequential fusion of VVOs

allows for transcellular transport, which is then utilized to transport the contents of the VVOs to the extravascular space. This transport mechanism serves the purpose of transporting proteins of 50-100 nm from the luminal area to the abluminal area of the endothelium. Although the precise activation mechanism is not fully understood, various factors such as histamine and VEGF-A have been reported to activate VVO transport upon exposure to the endothelium. Understanding the activation mechanism of VVO transport is crucial in developing therapeutic interventions that can prevent or treat the pathological conditions associated with the dysfunction of VVO transport [23,24].

The process of transportation involves another mechanism that is referred to as a paracellular process, as evidenced by several studies [24,25]. This event requires the temporary inhibition of cell-cell endothelial junctions and the release of several inflammatory mediators, including thrombin, histamine, proinflammatory cytokines, and VEGF, into the circulation These factors activate different signaling pathways, which include protein kinases, MAP kinases, and Rho GTPases, ultimately causing the interruption of cell-cell joints and the migration of phagocytic and other blood cells. Therefore, it is important to understand the mechanisms involved in this process to develop effective strategies to manage various diseases [23,24].

Vascular hyperpermeability has been recognized as a catalyst of the inflammatory cascade, facilitating the infiltration of inflammatory cells such as monocytes and macrophages into the extravascular space. These cells are capable of releasing a variety of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, which can further upregulate the expression of adhesion molecules and chemokines, thus promoting the recruitment of T-lymphocytes. The resultant amplification of the inflammatory response may ultimately lead to tissue damage and dysfunction [26]. Hypoxia is recognized as a crucial participant in the process of tumor angiogenesis, as widely acknowledged. The generation of hypoxia and the consequent release of Vascular Endothelial Growth Factor (VEGF) are influenced by various factors during the progression of cancer. These factors collectively contribute to the intricate mechanisms underlying tumor angiogenesis and the associated pathophysiology [27].

5. NSAIDS PROVEN TO HAVE ANTI-CANCER EFFECTS

The relationship between elevated COX-2 expression, inflammation in the microenvironment, and the aggressive nature of gastrointestinal malignancies has led to a great deal of research surrounding NSAIDs that possess both COX-2 dependent and -independent properties. Prominent among the drugs being evaluated are aspirin and celecoxib.

These two have received significant attention over the past decade due to their potential preventative and complementary effects in the treatment of colorectal and gastric cancer. Additionally, Tolfenamic acid (TA) and sulindac sulfide (SS) have been the subject of extensive research regarding their anti-tumorigenic properties among NSAIDs, due to their superior anti-cancer effects when compared to a multitude of other NSAIDs [28-30].

6. ASPIRIN AND ITS ANTI-CANCER EFFECT

While aspirin serves as an irreversible inhibitor of both COX-1 and COX2 enzymes, its impact is influenced by its brief half-life. This characteristic leads to the regeneration of COX isoenzymes within nucleated cells within a matter of hours. Consequently, the focal point of aspirin's principal influence is perceived to be on anucleate platelets. This influence manifests through the acetylation inhibition of COX-1 within platelets [31].

Circulating platelets are believed to play a role in the dissemination of tumor cells and the progression of metastasis. This is accomplished by their contribution to the interaction between tumor cells and the extracellular matrix, as well as their adhesion to endothelial cells in circulation. These platelets facilitate processes that include tumor cell immune evasion and the establishment of metastatic sites [32,33]. Numerous sizable epidemiologic studies have ascertained that the long-term administration of low dosage aspirin (75-300 mg/daily) can proficiently curb the prevalence of diverse forms of cancer, reduce the rate of malignant cancer metastasis, and furnish patients with a substantial chance of survival [34].

There is also clinical and epidemiological evidence suggesting the need for higher doses of aspirin or NSAIDs. Several COX-independent

pathways have been suggested as an alternative mechanism for the consistent efficacy of aspirin's inhibition of cell proliferation in COX-2 negative cancer cells [35]. In vitro investigations have demonstrated an analogous upregulation of COX in ovarian neoplasms, and administration of aspirin results in the curtailment of cellular proliferation and the triggering of apoptotic processes [36].

Study by Cuzick et.al Prophylactic aspirin use for at least five years at doses ranging between 75 and 325 mg/day appears to have a favorable benefit-to-harm profile. Longer usage periods are likely to result in more significant benefits. For individuals between 50 and 65 years of age and at average risk, the use of aspirin for ten years would result in a relative reduction of between 7% (in women) and 9% (in men) in cancer, myocardial infarction, or stroke events over a 15-year period. Additionally, there would be an overall 4% relative reduction in all deaths over a 20-year period [37].

7. IBUPROFEN AND ITS ANTI-CANCER EFFECT

Ibuprofen, A Non-Steroidal Anti-inflammatory Drug (NSAID) and is utilized to alleviate pain, fever, and various inflammatory conditions. The mechanism of action of ibuprofen involves the inhibition of cyclooxygenase (COX) activity, which is essential for the synthesis of prostaglandins (PG) [38]. It is believed that this particular action is responsible for the chemo preventive effect associated with the administration of ibuprofen [39].

The article by Paulo Matos et.al says that inflammation can elicit an upregulation of Rac1b expression in the colon, which is linked to the survival of tumor cells. Notably, the Non-Steroidal Anti-inflammatory medication ibuprofen was observed to suppress Rac1b expression in both inflamed colonic tissue and cultured tumor cells, resulting in a decrease in tumor cell viability and proliferation. These outcomes propose that ibuprofen may hold potential as a beneficial treatment option for patients with serrated colorectal tumors or inflammatory colon syndromes [40].

Ibuprofen can also reduce the activity of matrix metalloproteinases (MMPs) in gastric cancer stem cells. MMPs are known to play a crucial role in tumor migration and metastasis. The study by Fatemeh Mahmoodi et.al, found that treatment with ibuprofen led to a decrease in MMP activity in gastric cancer stem cells, which could potentially inhibit the metastatic ability of these cells. Overall, the results suggest that ibuprofen may have potential as a treatment for certain types of cancer [41].

8. CELECOXIB AND ITS ANTI-CANCER EFFECT

Over the course of more than two decades, Celecoxib, known for its selective inhibition of COX-2, has been employed as a medication for its, anti-inflammatory, analgesic, and antipyretic effects. Despite its widespread use, the antineoplastic properties of this drug have not received adequate investigation. However, there has been a significant surge in research studies examining the antineoplastic effects of Celecoxib in recent years [42]. Celecoxib selectively targets various proteins beyond COX-2, which play crucial roles in regulating cell viability and apoptosis [43]. Celecoxib also has the ability to regulate various molecules including FAK, Cx43, p21, and Ki-67 while concurrently blocking AKT activation. Celecoxib additionally participates in pathways encompassing COX-2, PGE2, EP2, p-AKT, p-ERK, and PGE2/NFkB. This engagement serves to hinder the invasion and metastasis of tumor cells [44,45].

Furthermore, Celecoxib demonstrates antagonistic properties towards antiapoptotic proteins like Mcl-1 and survivin. This characteristic underscore the potential significance of utilizing Celecoxib for addressing apoptosis-resistant tumors characterized by the overexpression of Bcl-2, Mcl-1, or survivin. This application could involve the administration of Celecoxib as a standalone treatment or in conjunction with radiotherapy, chemotherapy, or targeted proapoptotic agents that may otherwise be hindered by survivin, Bcl-2, or Mcl1 [46].

The Double-blind randomized study by Annelies Debucquoy et.al reveals that Patients treated with celecoxib exhibited a relatively improved response rate (61%) compared to those treated with placebo (35%), although this difference did not reach statistical significance (p=0.13). There were slight increases in Tdown staging and N-downstaging with celecoxib. Changes in plasma IL-6 levels and intratumoral COX2 or Ki67 resulting from chemoradiation were not further influenced by celecoxib treatment, and therefore these factors did not provide predictive value for treatment benefits. Combining celecoxib therapy

with chemoradiation did not introduce additional toxicity and appeared to help alleviate therapy-related pain [47].

9. CONCLUSION

The present review focuses on the potential impact of Non-Steroidal anti-inflammatory drugs (NSAIDs) on cancer treatment and prevention. NSAIDs are widely used for pain relief and inflammation control, and their use in cancer management has been a subject of significant scientific interest. The intricate relationship between inflammation, cancer development, and the potential role of NSAIDs in mitigating cancer-related processes is discussed in detail.

The review highlights the anti-cancer effects of specific NSAIDs, such as aspirin, ibuprofen, and celecoxib. Aspirin, for instance, has been associated with reduced cancer prevalence and metastasis owing to its role in inhibiting COX enzymes. Similarly, ibuprofen has been found to inhibit key signaling pathways and suppress tumor cell viability, especially in inflammatory conditions.

In conclusion, the evolving research in the field of NSAIDs and their impact on cancer treatment and prevention underscores the intricate connections between chronic inflammation, angiogenesis, and cancer progression. The potential of NSAIDs, particularly aspirin, ibuprofen, and celecoxib, to influence various aspects of tumor behavior is promising. However, further rigorous studies are required to establish their clinical efficacy and safety in diverse cancer scenarios. The use of NSAIDs as adjunctive therapies alongside conventional treatments presents a promising avenue for enhancing cancer management strategies.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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