INFLAMMATION IS RELATIVELY LINKED TO CANCER AND PLAYS A SIGNIFICANT ROLE IN TUMOR FORMATION AND PROGRESSION

Abstract

The mediators and cellular effectors of inflammation are important constituents of the local environment of tumours. In some types of cancer, inflammatory conditions are present before a malignant change occurs. Conversely, in other types of cancer, an oncogenic change induces an inflammatory micro-environment that promotes the development of tumours. Regardless of its origin, 'smouldering' inflammation in the tumour microenvironment has many tumour-promoting effects. Tumour-promoting inflammation is considered one of the enabling characteristics of cancer development. Chronic inflammatory disease increases the risk of some cancers, and strong epidemiological evidence exists that NSAIDs, particularly aspirin, are powerful chemo preventive agents. Tumour microenvironments contain many different inflammatory cells and mediators; targeting these factors in genetic, transplantable and inducible murine models of cancer substantially reduces the development, growth and spread of disease. Thus, this complex network of inflammation offers targets for prevention and treatment of malignant disease. Much potential exists in this area for novel cancer prevention and treatment strategies, although clinical research to support targeting of cancer-related inflammation and innate immunity in patients with advanced-stage cancer remains in its infancy.

Keywords: Cancer, Cells, Inflammation, Chemotherapy, Tumour, Immunosuppression

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I. INTRODUCTION

Inflammation is intricately linked to cancer, playing a significant role in both tumor formation and progression. Chronic inflammation contributes to carcinogenesis by stimulating tumor cell proliferation, angiogenesis, and metastasis, while concurrently diminishing responsiveness to the immune system and anti-cancer agents. A microenvironment rich in inflammatory cells, growth factors, and chemicals fosters DNA damage, fostering long-term cell proliferation and survival, thereby increasing the risk of cancer. Numerous epidemiological studies have underscored a noteworthy relationship between inflammation and cancer. Tumor cells exhibit a phenotype akin to inflammatory cells, producing cytokines, chemokines, and their receptors. The chronic synthesis of these inflammatory mediators can induce tissue and DNA damage, resulting in the accumulation of mutations in epithelial cells while accelerating their proliferation. Mutated cells release cytokines, attracting inflammatory cells and contributing to angiogenesis, migration, and metastasis, thus creating a cancer inflammatory microenvironment. Many anti-inflammatory medications, especially NSAIDs, can disrupt the tumor microenvironment by reducing cell migration and increasing apoptosis and chemosensitivity. Long-term NSAID use has been associated with a reduced risk of initial or recurring malignancies.

II. INFLAMMATION

Inflammation is a natural response to microbial pathogen infection and wound healing. Activated endothelium, macrophages, and mast cells situated in the tissues attract neutrophils to inflammatory regions by releasing appropriate mediators in response to tissue damage. Neutrophils serve as the initial effectors of inflammation, and their recruitment involves a four-step process: activation of P-, L-, and E-selectins to facilitate cell rolling along the vascular endothelium, activation of leukocyte integrins, neutrophil adherence to the vascular endothelium, and subsequent transmigration to the inflammatory sites.

[**ABBREVIATIONS: Inflamm** - INFLAMMATION; Ep - EPITHELIAL CELLS]

1. **Nomenclature:** The suffix 'itis' is commonly used to signify the nomenclature of an inflammatory lesion.

   Thus, inflamm of the appendix is referred to as appendicitis.

2. **Etiology:** There are many factors responsible for inflamm in an individual:

   - **Non-Infectious Factors**
     - **Physical:** Physical injury, ionizing radiation, trauma, Burn, foreign bodies,
     - **Chemical:** Alcohol, fatty acids, glucose, chemical irritants, toxins
     - **Biological:** Cell injury
     - **Psychological:** Exhilaration

   - **Infectious Factors**
     - **Viruses**,Bacteria and other microbes.

3. **Classification of Inflammation:** Inflammmay be classified as- 1. Acute and 2. Chronic

4. **Acute Inflammation:** Acute inflammation is the body's initial response to harmful stimuli, and it is characterised by an increase in the flow of plasma and leukocytes (especially granulocytes) from the circulation into the injured tissues.

5. **Prolonged Inflammation:** Chronic inflammation is inflammation that persists over an extended period. This results in a gradual transformation in the composition of cells at the inflammation site, including the presence of mononuclear cells. It is distinguished by the simultaneous destruction and repair of tissue through the inflammatory process. The migration of leukocytes from the circulation into the tissue enhances the inflammatory response.

6. **Symptoms:** Inflammation symptoms differ depending on whether the reaction is immediate or persistent. The abbreviation "PRISH" summarises the consequences of acute inflammation. They are as follows:

    - **Pain:** Chemicals that stimulate nerve endings are produced, increasing the sensitivity of the region.

    - **Swelling:** This is due to a fluid build-up.

    - **Redness:**This occurs because the capillaries in the area are filled with more blood than usual.

    - **Heat:** More blood rushes to the afflicted region, making it warm to the touch.

    - **Immobility:** There may be some loss of function in the inflamed area.

    These five acute inflame markers only apply to skin inflamms. Chronic inflammatory symptoms can be beneficial in a variety of ways. Examples include fatigue, fever, mouth sores, rash, chest discomfort, joint and stomach pain.

III. PATHOPHYSIOLOGY AND MOLECULAR MECHANIS OF INFLAMMATION

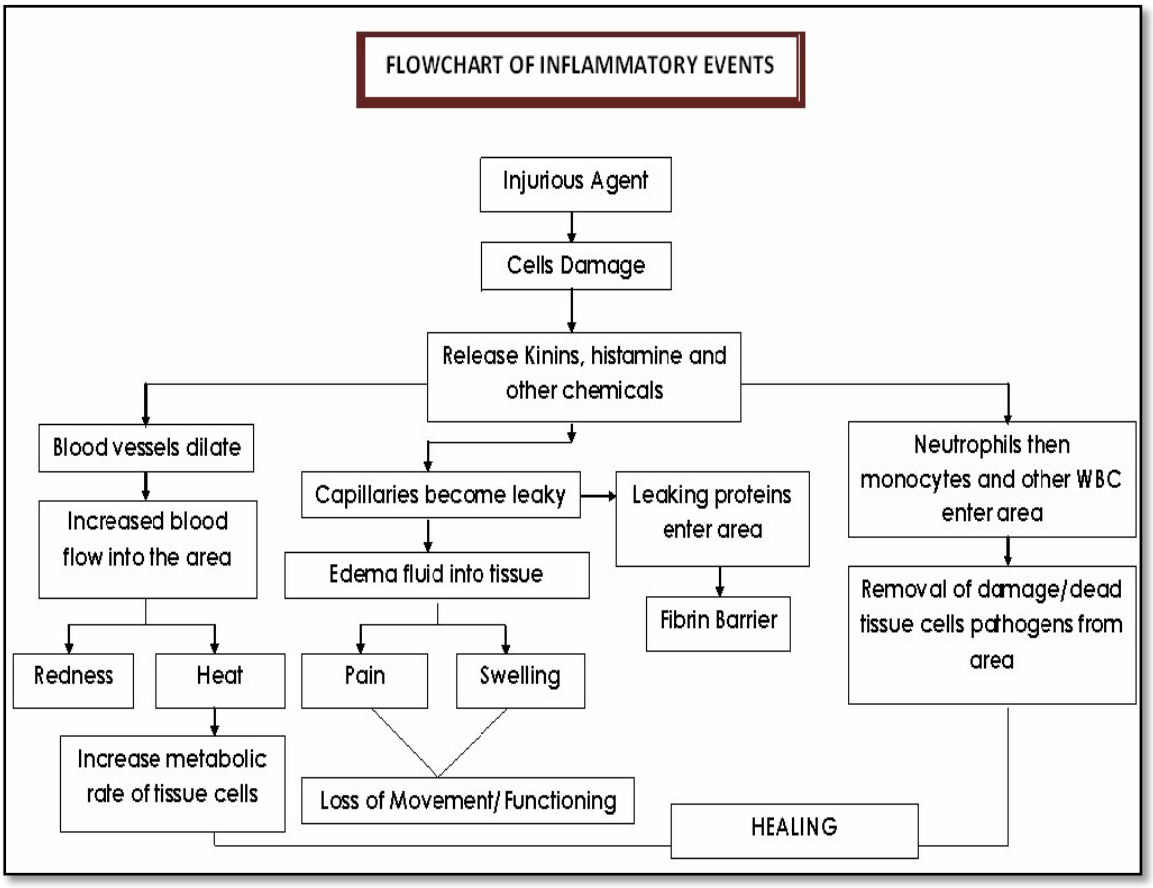


Figure 1: Pathophysiology of Inflammation

Initially, host cells detect inflamm through transmembrane receptors called pattern-receptors, which are produced by both innate and adaptive immune cells.

They do this by identifying structures conserved in microorganisms known as pathogen-associated molecular patterns (PAMPs) and endogenous chemicals derived from internal damage known as hazard-associated molecular patterns (DAMPs). . The second step involves maturation of IL-1 by caspase-1-mediated cleavage of pro-IL-1. This requires a 'caspase-1-activating' high-molecular-weight complex known as the inflammasome.

Members of the NK-κB family share structural similarity with the retroviral oncoprotein v-Rel at the N-terminus known as the Rel homology region (RHR), forming stable homodimers and heterodimers. It promotes the generation of amomers. In response to stimulation, NK-κB dimers are released into her IB cytoplasm and translocate to the nucleus, where they trigger specific gene expression. In addition to NK-κB, several other transcription factors play important roles in selective activation of inflammatory genes. Activator protein-1 (AP-1), to name a few, is a heterodimer of the basic leucine zipper proteins c-Jun and c-Fos. Cyclic-AMP (cAMP) Response Element Binding Protein (CREB), cAMP inducer. E2F, a transcription factor activated by the adenoviral E1A protein in adenovirus-infected cells.

Serum response factor (SRF) and related ternary complex factor (TCF) involved in serum induction of Fos transcription (Dalton et al., 1992). **"Figure - 1"** shows a schematic diagram of the pathophysiology of inflammation.

IV. INFLAMMATION AND CANCER

Several epidemiological and clinical studies have shown associations between inflammation and cancer. For example, ulcerative colitis and Crohn's disease (Seril et al., 2003) may increase tumor risk, whereas anti-colitis drugs may minimize this process (Qiu et al. 2017). Additionally, microbial agents or chemical irritants often cause inflammation. For example, Helicobacter pylori infection or Hepatitis B and viruses can predispose to cancer (Van Tong et al., 2017).

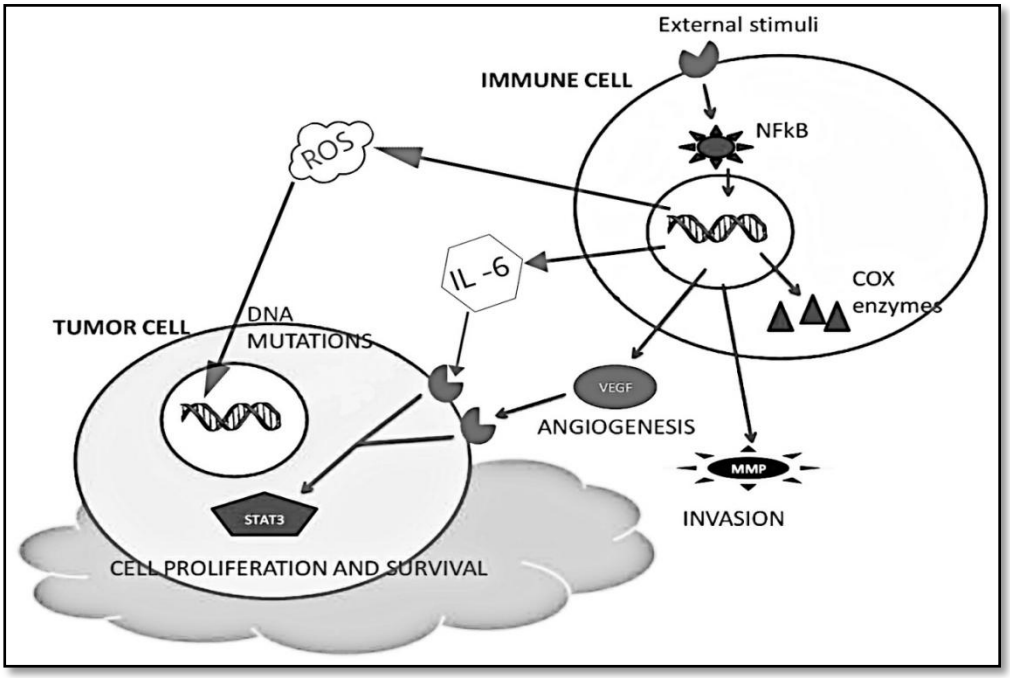


Figure 2: Inflammation and Cancer

A variety of inflammatory and carcinogenic agents can activate the transcription factor NF-kB. IL-6 and growth factors induce STAT3 activation leading to cell proliferation and survival, whereas metalloproteases degrade membrane substrates and promote cell invasion. In addition, macrophages secrete numerous reactive oxygen species (ROS) and antimicrobial mutagens. They cause DNA alterations that induce persistent tissue damage and contribute to tumorigenesis. These cytokines released at the tumor site are intrinsic signals for lymphocyte recruitment, but their importance in tumor progression is unknown mutant cells can create a tumor inflammatory environment enriched with macrophages, neutrophils, eosinophils, dendritic cells, mast cells and lymphocytes, all of which play important roles in inflammatory malignancies. increase. Tumor-associated macrophages (particularly TAMs) contribute to angiogenesis and promote tumor growth by secreting specific factors such as cytokines and growth factors, endothelin-2, and urokinase-type plasminogen activator that

suppress immune responses. Can facilitate progress. **“Figure - 2”** shows a schematic diagram of inflammation and cancer.

V. THE ORIGINS AND TYPES OF INFLAMMATION IN CANCER

Inflammation may play an important role in cancer, from the onset of the malignant phenotype to metastatic progression **"Figure - 3” and** metastases in distant places **"Figure - 4"**.

1. **Inflammation Arising from Infection, Autoimmunity or The Environment :** There are many examples of inflammation that contribute to the onset of cancer, including (1) infectious agents that directly cause cancer, e.g. feline leukemia virus, or inflammatory viruses, eg. : Helicobacter pylori causes mucosal-associated lymphoma (MALT) or gastric carcinoma in humans (De Falco et al., 2015); (2) immune-mediated diseases that promote chronic inflammation, e.g. inflammatory bowel disease IBD and colon cancer; (3) subclinical inflammation, for example: obesity causes inflammation and leads to liver cancer; (4) environmental carcinogens, e.g. smoke pollution (Cohen et al., 1995).

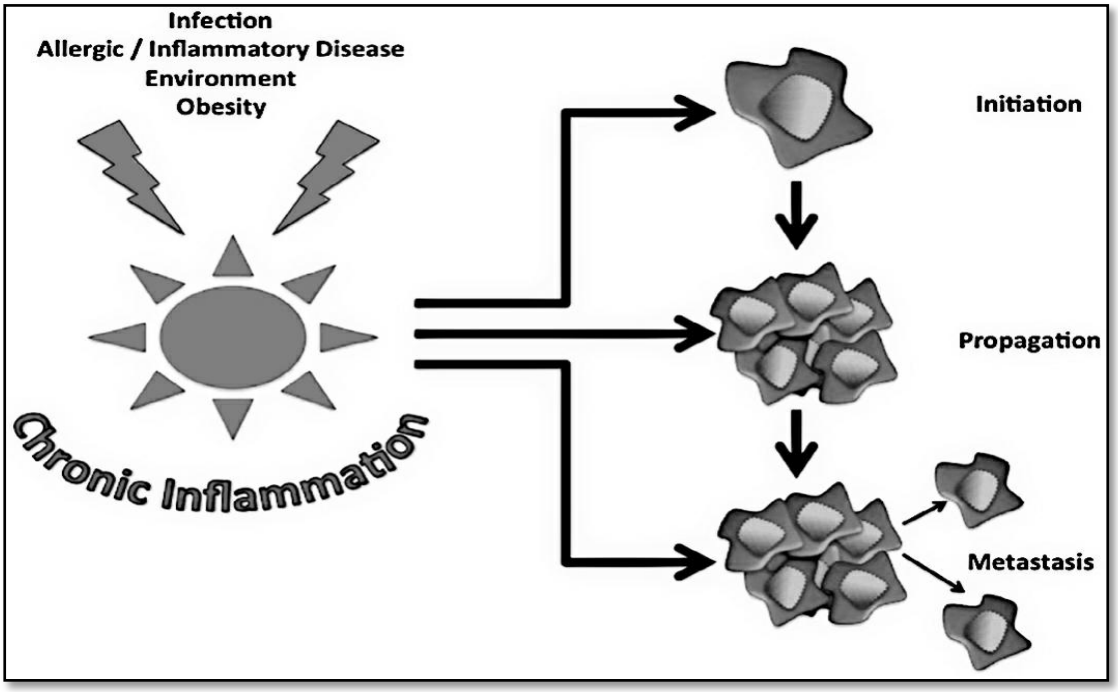


Figure 3: Role of Inflammation in Cancer

2. **Inflammation Arising from Tumours:** The microenvironment maintains a persistent inflammatory state once tumors are established. Tumors elicit an innate inflammatory response and proto-tumoral microenvironment supported by macrophage infiltration and regulated by chemical mediators such as interleukins IL-8 and IL-10. Cell Infiltration, Cytokines, Chemokines : (1) It is proangiogenic and promotes angiogenesis in cancer ; (2) act as a growth factor for tumor cells ; (3) promotes epithelial-to-mesenchymal transition (EMT).

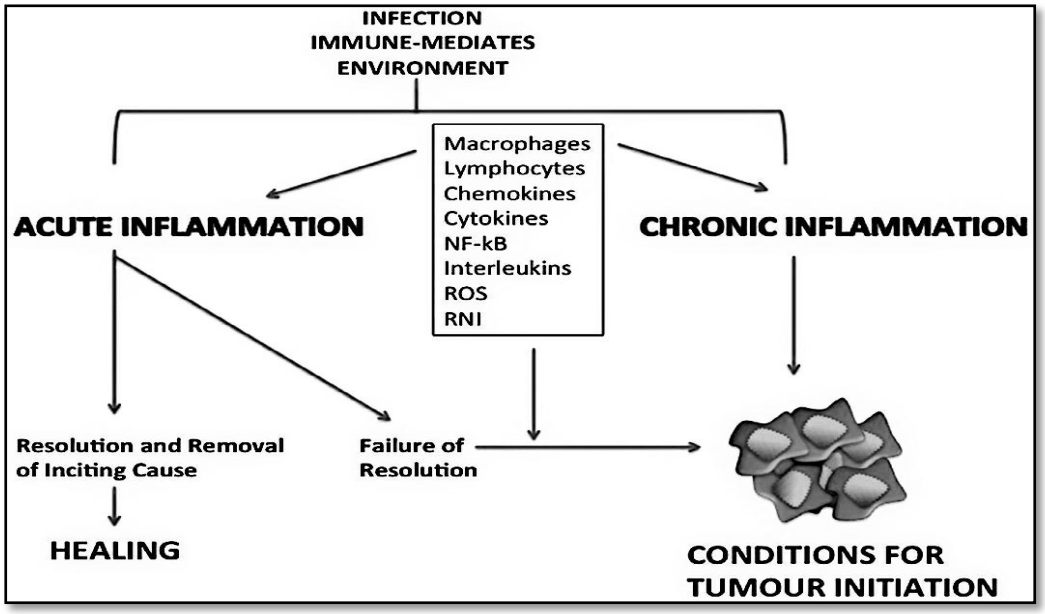
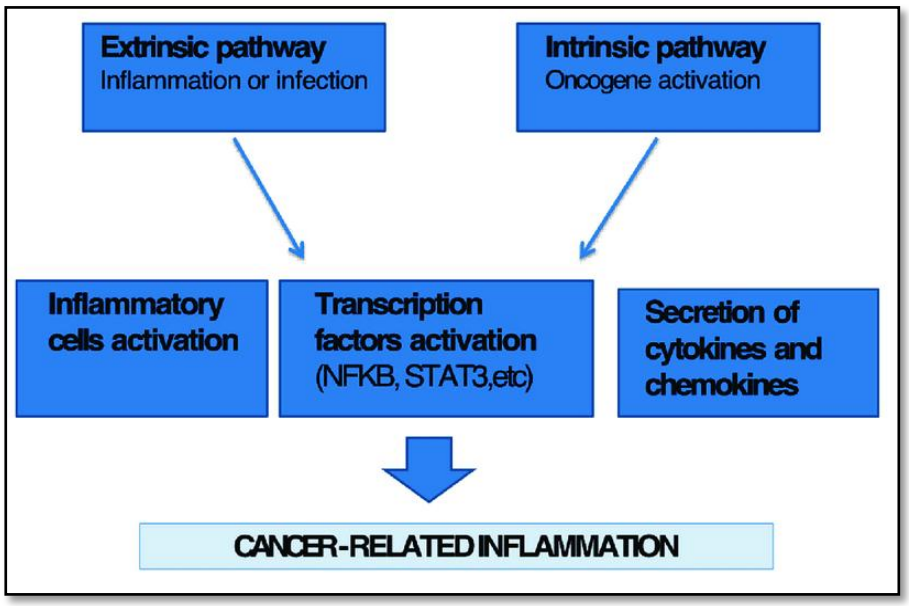


Figure 5: Tumour Initiation through the Effects on DNA

VI. THE KEY MEDIATORS OF INFLAMMATION

There are two mechanisms that link inflammation and cancer. Exogenous and endogenous **("Figure - 6")**. Upon activation, NF-kB secretes inflammatory mediators, growth factors, and metalloproteases that contribute to the establishment of the inflammatory tumor microenvironment (Sebiomo et al., 2011). For example, cytokines, growth factors, and differentiation factors involved in regulating immune cell proliferation and differentiation contribute to cancer by activating cell proliferation and inhibiting and inhibiting apoptosis of damaged cells (Lee et al. , 1986; Penna et al., 2003) through different molecular signaling cascades.



VII. TUMOR NECROSIS FACTOR ALPHA (TNF-ALPHA)

It can also suppress the expression of adiponectin, glute-4, PPAR-, and perilipin in adipocytes. Studies have shown that TNF-α produces additional pro-inflammatory cytokines such as IL-1 and IL-8 in her Caco-2 or HT-29 cell lines.

1. **Histamine:** Histamine is a vasodilator, smooth muscle constrictor, and stimulator of vascular permeability, respiratory mucus, and stomach acid production.

2. **Leukotrienes:** The biologic combination, also known as the anaphylactic slow-reacting substance, is made up of leukotriene (LT) C4 and its derivatives, LTD4 and LTE4.

3. **Prostaglandins:** Prostaglandins are another type of arachidonic acid-derived molecule that mediates allergic responses. Human mast cells produce PGD2 after being triggered by the Ig-E receptor or a calcium ionophore.

4. **Cytokines and Chemokines:** Cytokines such as IL-1, -2, -4, -5, -6, and GM-CSF impact the development of allergic inflamm by influencing the activity of inflammatory cells such as eosinophils, macrophages, B cells and T cells.

5. **iNOS and No Secretion :** iNOS is an enzyme that interferes with NO production and is overexpressed in variations of chronic inflammatory and cancer processes. Activation of iNOS by proinflammatory cytokines or NFkB causes DNA damage, reduces DNA repair, and promotes cancer development (Hussain et al., 2004).

6. **LOX and COX Pathways:** 5-LOX has been detected in human or animal cancer cell lines such as brain, breast, colon, kidney, mesothelium, esophageal mucosa, pancreas, and prostate, and most of these investigations also increased 5-LOX products. I'm here. A recent study (Kummer et al., 2012) shows that 5-LOX expression in papillary thyroid carcinoma (PTC) promotes carcinogenesis through induction of metalloproteinases (MMPs). These enzymes are of two types

    - **COX-1,** is constitutively expressed in many cells and is primarily involved in the physiological production of prostanoids.
    - **COX-2,** Its expression is often induced in cells in inflammatory conditions.

7. **JAK/STAT Pathway :** The STAT3 (signal transducer and activator of transcription 3) protein is a constitutive transcription factor present in a variety of human cancers, including multiple myeloma, leukemia, lymphoma, breast cancer, prostate cancer, and squamous cell carcinoma of the head and neck (Hodge et al., 2005).

8. **CREB Signaling Pathway:** Cell survival, neuron growth, and metabolism all rely on CREB. For example, CREB-mediated gene expression is necessary for nerve growth factor (NGF)-induced cell survival, which improves sympathomimetic neuron survival by activating downstream target genes (Salojin et al., 2007).

VIII. THE ROLE OF INFLAMMATION IN TUMOUR INITIATION AND MAINTENANCE

Tumor products have an impact on inflammatory conditions; immunosuppressive cytokines allow immune evasion and the recruitment of tumor-promoting inflammatory cells such as myeloid-derived suppressor cells, regulatory T cells, and tumor-promoting (M2) macrophages **"Figure -7"**. The tumour microenvironment is a complex network of interactions between tumour cells, supporting stroma, and inflammatory cells that collaborate to maintain the malignant phenotype **"Figure - 8"**. Cancer and inflammation are intricately linked **("Table - 1").**

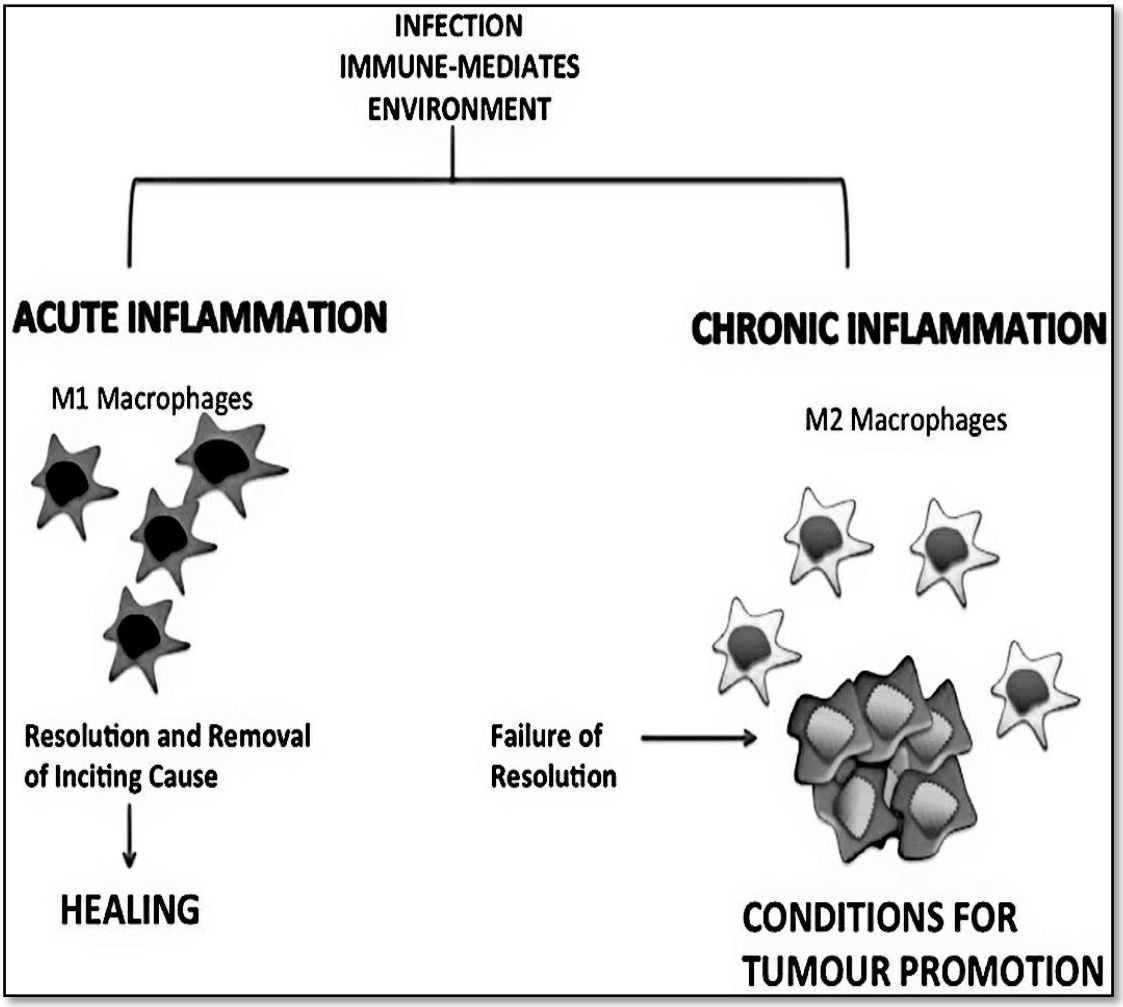


Figure 7: Two Ends of A Phenotypic Spectrum of Macrophages

IX. BRIDGING CANCER AND INFLAMMATION

After exposure to pathogens, innate and specific immune responses can work together to eliminate the source of infection and avoid additional tissue damage during acute inflammation. This not only prolongs immune cell infiltration, but also leads to the formation

of reactive oxygen species (ROS), reactive nitrogen species (RNA), and macrophage migration inhibitory factor (MIF), all of which can cause DNA damage.

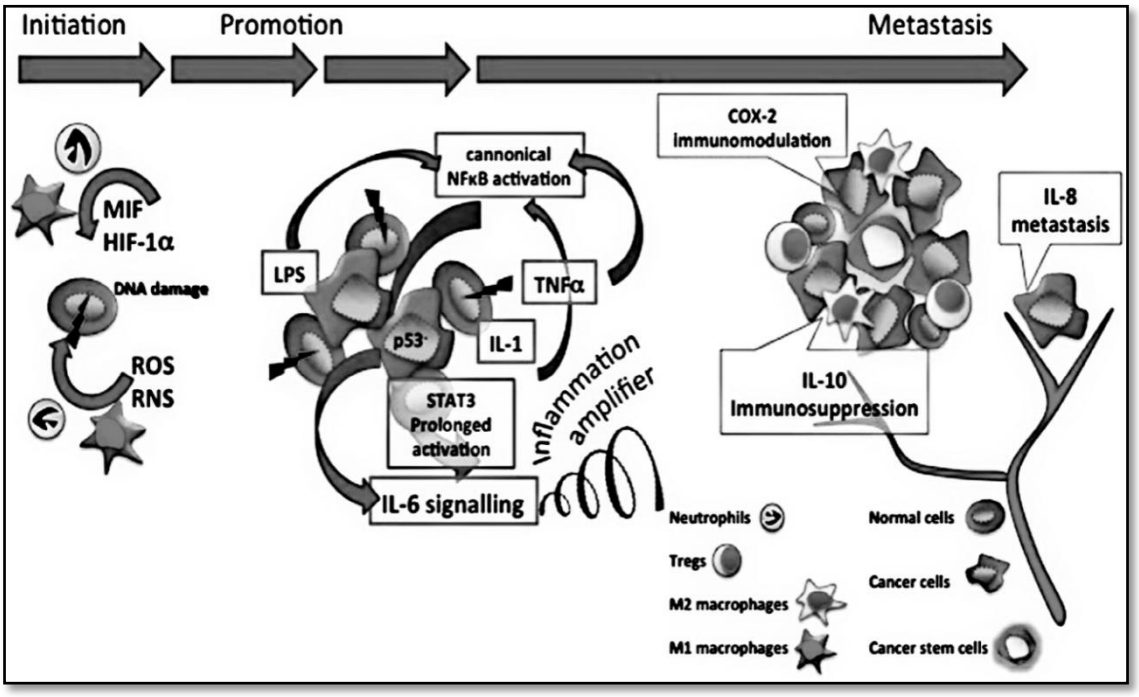


Figure 8: Summary of the Cells and Mediators within The Tumour Microenvironment

Central Role of NF-κB : NF-κB is important in regulation of the immune response to infection, and its dysregulation has related to illnesses such as autoimmunity and cancer. This molecule's critical involvement in cancer may be summarised as follows : (1) constitutive NF-κB expression has been identified in many cancer types, supporting its role in promoting the cancer phenotype ; (2) dysregulation of the NF-κB pathway has documented in haematological malignancies and lymphoma; these lymphoid malignancies feature aberrant NF-κB activation, which promotes tumorigenic cell survival, protects against apoptosis and favours oncogenesis ; (3) Constitutive NF-κB activation is a characteristic of chronic inflammatory illness, which is connected to an elevated risk of cancer. ; (4) The primary cause of dysregulation of the NF-κB signalling pathway in human non-lymphoma Hodgkin's (NHL) includes chromosomal abnormalities (e.g. Epstein Barr virus, human T-cell leukaemia virus-1) ;

(5) Up-regulation of anti-apoptotic Bcl-2 family proteins as a result of persistent activation of the NF-κB pathway ; (6) The development of resistance in the cytotoxic effects of chemotherapeutic drugs is a serious barrier to current cancer therapy. Many chemotherapeutic drugs that induce p53-mediated apoptosis also activate NF-κB.

NF-κB inhibition increases the effectiveness of anticancer drugs and decrease the incidence of resistance to these treatments in numerous in vivo and in vitro models, making NF-κB a prospective therapeutic target in oncology. Thus, the NF-κB signaling pathway is involved in complex interactions with many cancer signaling pathways (protein kinases, c-Jun N-terminal kinase, STAT3, and transcription factors such as p53),

potentially Concerns have been raised about its use. Use of NF-κB inhibitors for cancer treatment with unforeseen side effects.

X. INFLAMMATION AS TARGET FOR CANCER PREVENTION

Since inflammation can predispose to tumorigenesis, targeting inflammation and molecules involved in inflammatory processes (COX-2 cyclooxygenase 2, NF-kB, VEGF) may be beneficial for cancer prevention and treatment method **("Table – 1")**.

1. **NSAIDs:** Cancer prevention by NSAIDs works by interfering with the eicosanoid system. NSAIDs are less toxic than conventional chemotherapy, have non-specific effects, and can reduce tumorigenesis by interacting with the tumor's inflammatory microenvironment.

   Several studies have shown that anti-inflammatory drugs can improve apoptosis and sensitivity to standard treatments while reducing invasion and metastasis (Ma et al., 2016; Saito et al., 2015; Yang et al., 2008), leading them to promising alternatives. for cancer treatment.

2. **Corticosteroids:** Corticosteroids are effective in reducing the side effects of chemotherapy and radiation therapy, and some studies have shown significant benefits in fighting cancer, either alone or in combination. Dexamethasone therapy enhanced the antitumor efficacy of conventional drugs in various animal cancer models (Zhang et al., 2008).

Table 1: Preventive and Anticancer Effects o f Anti-Inflammatory Drugs

Sl No.	Drug	Effect
1	**ASPIRIN**	Induced activation of NF-kB pathway in colon cancer cells, Preventive effect on bladder cancer, breast cancer, colorectal cancer, esophageal cancer, lung cancer
2	**COLECOXIB**	Induced apoptosis in prostate cancer cells, Preventive effect on bladder cancer, breast cancer, colorectal cancer, esophageal cancer, lung cancer, cervix cancer, neuroblastoma
3	**DEXAMETHASONE**	Induced cell death in multiple myeloma mediated by miR-125b expression Preventive effect on breast cancer, rectal cancer, multiple myeloma

4	**IBUPROFEN**	Inhibited activation of nuclear β-catenin in human colon adenomas, Preventive effect on breast cancer
5	**PIROXICAM**	Prevented colon carcinogenesis by inhibition of membrane fluidity and canonical Wnt/β-catenin signaling, Preventive effect on colorectal cancer
6	**SULINDAC**	Induced activation of NF-kB pathway in colon cancer cells, Preventive effect on breast cancer

XI. ANTI-CANCER EFFECTS OF ANTI-INFLAMMATORY AGENTS

Several preclinical and clinical studies have shown that a combination of chemotherapeutic and anti-inflammatory agents improves patient prognosis. Although the mechanism of action behind the anti-cancer effects of anti-inflammatory drugs is unknown, three major possible processes have been characterized.

1. **Chemoprotection :** The side effect profile of standard anticancer therapies is one of the difficulties. Chemotherapy often causes toxicity to both the tumor and various normal tissues, reducing the patient's quality of life. Some studies have shown that combining conventional treatments with anti-inflammatory drugs can reduce the side effects of chemotherapy. For example, in patients with metastatic prostate cancer, combined treatment with celecoxib and docetaxel reduced myelotoxicity (Calaluce et al., 2000), whereas celecoxib combined with FOLFIRI (folinic acid, fluorouracil, and irinotecan) or capecitabine diarrhea (Baron et al., 2003). The GECO (gemcitabine-coxib) study evaluated the effect of celecoxib in combination with gemcitabine in patients with NSCLC and found that 3 months of celecoxib treatment improved quality of life. Another glucocorticoid, budesonide, has been used in combination with irinotecan to reduce episodes of diarrhea (Zhao et al., 2017).

2. **Alterations in Pharmacokinetics Or Metabolism:** Anti-inflammatory drugs can alter the pharmacokinetics of other drugs. Glucocorticoids do not affect plasma pharmacokinetics, but alter the absorption of gemcitabine or carboplatin from the spleen and bone marrow, increasing the number of drugs reaching the tumor. In addition, anti-inflammatory drugs may affect chemotherapy metabolism. For example, rofecoxib acts as a CYP1A2 inhibitor (Wang et al., 2004), causing changes in the concentration, half-life, and clearance of other drugs metabolized by CYP1A2. Dexamethasone increases her CYP2D6 activity, which celecoxib decreases (Yano et al., 2006), impairing the efficacy of the CYP2D6 substrate tamoxifen. Diclofenac inhibits DMXAA glucuronidation by inhibiting its metabolism and increasing plasma concentrations (Freshney et al., 1986).

3. **Chemosensitization :** In addition to the ability of anti-inflammatory agents to reduce the toxicity of conventional treatments by altering metabolism, the beneficial anticancer effects of combinations of anti-inflammatory and chemotherapeutic agents are likely due to chemo-sensitization of anti-inflammatory agents. Thing. Several preclinical studies have shown that celecoxib is additive or synergistic in vitro when combined with etoposide, doxorubicin, vincristine, or irinotecan. Notably, celecoxib in combination with irinotecan or doxorubicin suppressed tumor development in a neuroblastoma rat model. Furthermore, celecoxib sensitized prostate cancer cells to docetaxel in vitro and in vivo and sensitized gliomas to radiation (Gerber et al., 1998).

Multiple studies have shown that NSAIDs promote apoptosis in multiple tumor types by directly acting on the NF-kB pathway. Aspirin and sulindac can bind to NF-kB in the nucleolus and inhibit transcription of NF-kB targets such as cytokines, growth factors and adhesion molecules. Celecoxib enhanced the antitumor effect of doxorubicin by increasing IkB expression and decreasing NF-kB activity (Gerber et al., 1998). Dexamethasone also inhibits the NF-kB pathway (Xiao et al., 2011).

Anti-inflammatory drugs can kill cancer cells by interfering with proteins involved in programmed cell death. For example, celecoxib enhanced the efficacy of docetaxel by activating caspases and PARP while reducing XIAP activity. Aspirin reduces NF-kB activity by inhibiting caspases and pro-apoptotic proteins, possibly interfering with the proteasome. According to Dittmann et al. Cancer cells can be exposed to radiation by suppressing EGFR in a COX-2-independent manner (Liang et al., 2007).

XII. NOVEL ANTI-INFLAMMATORY DRUGS WITH ANTI-CANCER ACTIVITY

Several clinical studies have been conducted evaluating the use of anti-inflammatory drugs in combination with chemotherapy regimens for cancer prevention and treatment, and anti-inflammatory drugs have shown promising efficacy and toxicity results.

1. **Anti-Cancer Agents Based On COX-2 Inhibitors:** Several studies evaluating the use of COX-2 inhibitors in cancer therapy have shown that the antitumor effects of these agents are independent of their ability to inhibit COX-2. (Rose-John et al. al., 2006).

2. **No-Donating Nsaids :** NO-donating NSAIDs are NSAID analogues with fewer side effects. These drugs retain the active ingredient that produces the anti-inflammatory effect and are attached to NO via a spacer. NO-NSAIDs containing aromatic spacers were more potent than those containing aliphatic spacers. Once produced, NO protects the gastrointestinal tract from damage caused by active drugs by reducing gastrointestinal toxicity (Stetler-Stevenson et al., 1999). NO-donating compounds were made by modifying diclofenac, naproxen, aspirin, sulindac, and ibuprofen (Lau et al., 2017). Several NO-donating NSAIDs caused apoptosis, growth inhibition, or cell cycle arrest in various forms of cancer in vitro and in vivo (Scotton et al., 2002; Kulbe et al., 2005). All preclinical studies of NO-donating NSAIDs have shown higher efficacy than NSAIDs, but further studies are needed to fully realize their potential in cancer prevention (Kim et al., 2016). NO-ASA (NO-acetylsalicylic acid) showed synergistic or additive benefits in

combination with oxaliplatin or 5-fluorouracil in colon cancer models and reduced cancer risk in induced pancreatic cancer models. Furthermore, the NO-ASA ortho- and para-isomers were more effective than the meta-isomers in reducing colon cancer cell proliferation and survival. The use of NCX4016 (NO-acetylsalicylic acid) for colorectal cancer prevention was investigated in phase I, but the study was terminated prematurely due to the suspected genotoxicity of the compound (Wang et al., 2010).

3. **Natural Products:** Grapes/red wine (resveratrol), garlic (various chemicals), and curry powder are all anti-inflammatory foods or natural products (curcumin). Produced anticancer effects on cancer cells or xenografts. These chemicals act as anti-inflammatory agents by inhibiting VEGF or COX enzymes or by targeting NFKB, MAPK, and JNK signaling pathways, and their activity contributes to their anticancer activity. It is possible (Yung et al., 2018; Cuello et al., 2001). .

   Garlic compounds have been shown to enhance the anticancer effects of cytarabine and fludarabine in myeloid leukemia cells (Song et al., 2009) and improve the sensitivity of prostate cancer cells and xenograft tumors to docetaxel with fewer side effects. (Putilnik et al., 1999).

4. **LOX Inhibitors :** Many researchers have proposed 5-LOX inhibitors (Zileuton, ZYflo, ABT-761) (Liu et al., 1998; Yeung et al., 2013), FLAP inhibitors (MK-886) (Frankel et al., 1996) used pharmacological tools such as Gao et al., 2015) or LTA4 hydrolase (Hu et al., 2001) and LTs antagonists (zafirlukast and montelukast) (Forsythe et al., 1996; Tan et al., 2006) block cell proliferation. Anti-LTs therapies that increase and induce apoptosis show promise for cancer prevention and treatment, but few clinical studies have been conducted to evaluate the efficacy of 5-LOX inhibitors in antitumor therapy. Treatment with LOX inhibitors dramatically inhibited cell proliferation in several pancreatic cell lines. In vivo experiments using athymic mice showed that LOX inhibitors suppress tumor growth and have potential applications in the prevention and treatment of pancreatic cancer.

   Gosh found that inhibition of his 5-LOX by her MKAP1, a FLAP inhibitor, caused apoptosis in LNCaP and PC3 cell lines. 5-LOX inhibitors induced apoptosis in esophageal cancer cells, whereas 12-LOX inhibitors showed anti-proliferative and pro-apoptotic effects on gastric cancer cells. Finally, several experiments with hematopoietic cells showed that the inhibitor 5-LOX AA861 caused apoptosis in the leukemia cell line P388.

5. **Embelin and Its Derivatives:** Embelin is a benzoquinone derivative that can impair arachidonic acid metabolism. Its structure consists of a 2,5-dihydroxy-1,4-benzoquinone polar core linked at the 3-position to a long hydrophobic alkyl chain that confers solubility in polar phases and allows the molecule to cross cell barriers. It has been. Collaborative research with professor Oliver Werz (University of Jena, Germany) showed that this molecule can inhibit both 5-LOX and mPGES-1 activity with IC50 values of 0.06 and 0.2 μM, respectively. Chronic structure of the membrane is important for inhibitory effects. This molecule has been shown to be able to block enzymes without going through the hydroquinone reduction pathway. Docking experiments showed that

embelin does not behave like an iron chelator, but fits with its non-decylated chain into the hydrophobic channel where the iron-catalyzed oxygenation process of AA normally takes place. The benzoquinone ring forms hydrogen bonds with three amino acids (Gln363, Gln557, and Tyr181) to maintain contact between enzyme molecules. Two water molecules that co-crystallize with the complex and form hydrogen bonds with two amino acids, Asn425 and Thr364, facilitate the interaction between embelin and 5-LOX. Recent studies have shown that emberin and its derivatives have antioxidant properties. **"Figure - 9"** shows a schematic diagram of anticancer effects of embelin.

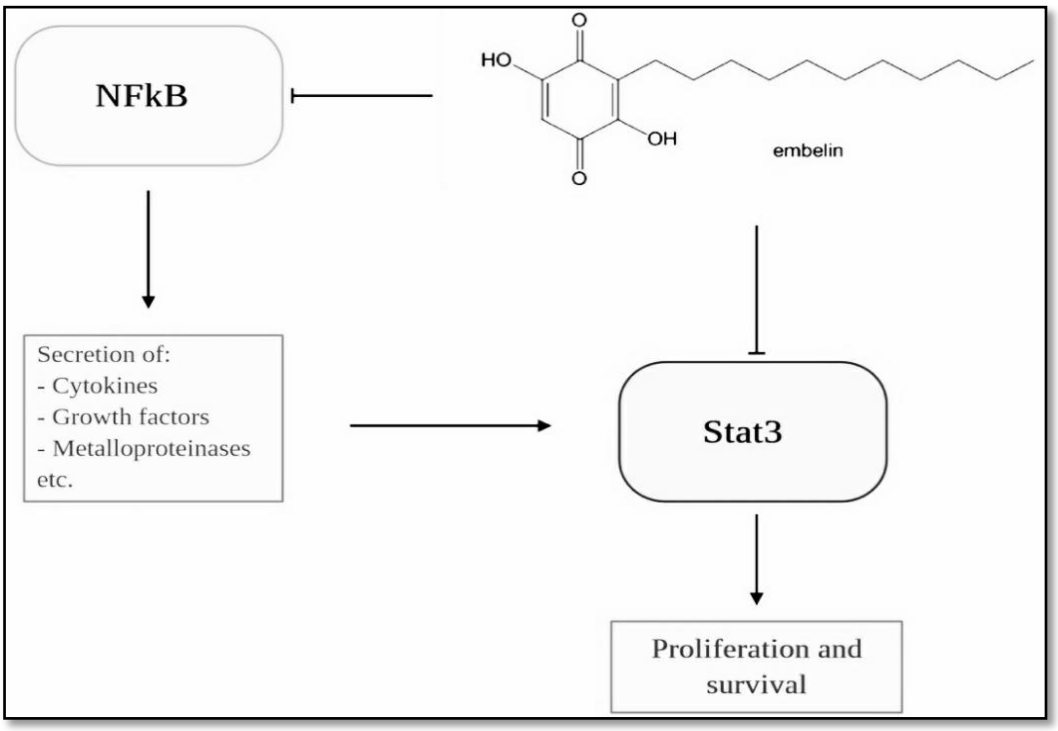


Figure 9: Anticancer Effects of Embelin

XIII. CONCLUSION

Inflammation is closely associated with cancer and plays an important role in tumor growth and progression. Therefore, there is a need to target inflammation alone or in combination with chemotherapeutic agents for cancer prevention and treatment. Many anti-inflammatory drugs can be used as adjuncts to conventional therapy, but further research is needed to fully exploit the potential of anticancer agents. Early detection and treatment of chronic inflammation can help prevent cancer from developing. Widespread off-target effects and toxicity limit the use of FDA-approved anti-inflammatory drugs in cancer therapy. A better understanding of the critical role of inflammation in cancer is needed to develop more effective alternative therapies.

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