



A Concise Review of Inflammatory Biomarkers Targeted Cancer Therapy

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Abstract

Inflammation is considered a general protective reaction of localized tissue against injury, irritation, or swelling. Inflammation may be acute, which is part of the defensive response; or chronic, which may lead to the development of various diseases including cancer. Several pro-inflammatory genes play important role in the various cellular processes like cell proliferation, angiogenesis, metastasis, and suppression of apoptosis. These pro-inflammatory genes include TNF- α , interleukins, chemokines, MMPs, cyclooxygenase, lipoxygenase, iNOS, Jak/STAT pathway, etc. All these genes are mainly regulated by the transcription factor NF- κ B, which is found active in many types of neoplastic cells. Therefore, developing molecules that target pro-inflammatory genes or transcription factor is believed to be one of the good strategies for development of anti-cancer agents. Literature data suggest that many anti-inflammatory agents, including non-steroidal anti-inflammatory drugs, corticosteroids, statins, metformin, embelin, and some natural products, can interfere with the tumor microenvironment by inhibiting pro-inflammatory genes or transcription factors and increasing cell apoptosis. This review describes the link between inflammation and cancer, the role of pro-inflammatory genes and transcription factors in the development of tumor cells, and the use of anti-inflammatory agents in cancer.

Keywords

anti-inflammatory agents, cancer, cancer prevention, inflammation, inflammatory biomarkers

List of abbreviations

TNF: tumor necrosis factor;	PG: prostaglandin;
COX: cyclooxygenase;	VEGF: vascular endothelial growth factor;
IL: interleukins;	JAK: janus kinase;
MMPs: matrix metalloproteinases;	STAT: signal transducer and activator of transcription protein;
LOX: lipoxygenase;	PI3K: phosphoinositide-3-kinase;
iNOS: inducible nitric oxide synthase;	SCC: squamous cell carcinoma;
HIF: hypoxia inducible factor;	NSAIDs: non-steroidal anti-inflammatory drugs; HCC: hepato-
PI3K: phosphoinositide-3-Kinase;	cellular carcinoma;
MAPK: mitogen activated protein kinase;	CDK: cyclin-dependent kinases

INTRODUCTION

In 1863, the first clue between inflammation and cancer was identified by Rudolf Ludwig Carl Virchow that the inflammatory process is one of the conditions for the development of cancer cells.^[1] Chronic inflammation triggers the growth of the tumor cells by accelerating the production of growth factors as well as reactive oxygen and nitrogen which interact with DNA and produce mutations. There are different inflammatory modulators like chemokines, cytokines, growth factors, free radicals, prostaglandins, and proteolytic enzymes that favor the development of the tumor cells. These inflammatory modulators are synthesized from different types of cells such as fibroblasts, adipocytes, dendritic cells, natural killer cells, lymphocytes, neutrophils, macrophages, etc. Some of these modulators directly act on tumor cells by supporting proliferation, oncogenic mutation, and inhibiting cell death. Some of the modulators act as prototumorogenic agents, which act on the components of the tumor microenvironment. The inflammation may be acute or chronic. The acute inflammation occurs for a short period as a pyrogenic response which results in the development of a fever for a short period. When inflammation lasts too long, then it can be chronic inflammation, which can be harmful and may lead to a disease.^[2] Various epidemiological studies suggest that 20% of all cancers begin as a direct consequence of a chronic inflammatory disease. Inflammation is the common process of various cancer risk factors, which include smoking, alcohol consumption, obesity, several types of infection, etc. (Fig. 1). The goal of primary, secondary, or tertiary cancer prevention is to reduce the exposure of risk factors of the cancers. Avoiding exposure to primary carcinogenic factors has the potential to reduce 30% of cancer deaths.^[3]

Prevention of cancer can be possible in two ways; the first is primary prevention by reducing exposure of risk factors of cancer and the second is by immunoprevention and

chemoprevention. Immunoprevention aims to control the development (or initiation) of cancer cells by the immune system while the chemopreventive effect focused on suppressing or prevent the conversion of malignant to invasive cancer types. In this review we had discussed, the role of various inflammatory mediators involved in the promotion of tumor which gives an idea about the link between inflammation and cancer and the role of anti-inflammatory agents in the treatment of cancer.^[4]

Various inflammatory mediators involved in the promotion of tumor

There are mainly two pathways that link inflammation and cancer: these are the intrinsic pathways and the extrinsic pathways. The first type of pathway is activated by inflammatory stimuli which increase the risk of cancer, and the second is due to genetic mutation which causes inflammation and cancer. This pathway is interconnected through various inflammatory mediators, which include various cytokines, growth factors, and metalloproteases (Table 1) which helps in the development of the tumor microenvironment (Fig. 2).

TNF-alpha

TNF-alpha is a multicellular kinase that plays important role in various cellular events like cell differentiation, survival, and death. There are two types of this receptor; the first is TNFR1 that is expressed all over the cell and the second is TNFR2, which is expressed mainly in the immune cells. TNFR1 receptor contains the intracellular domain, the transmembrane domain, an extracellular domain, and it is considered as one of the important members of the death receptor family as it is mainly involved in the cell death program. Due to this, it is also considered

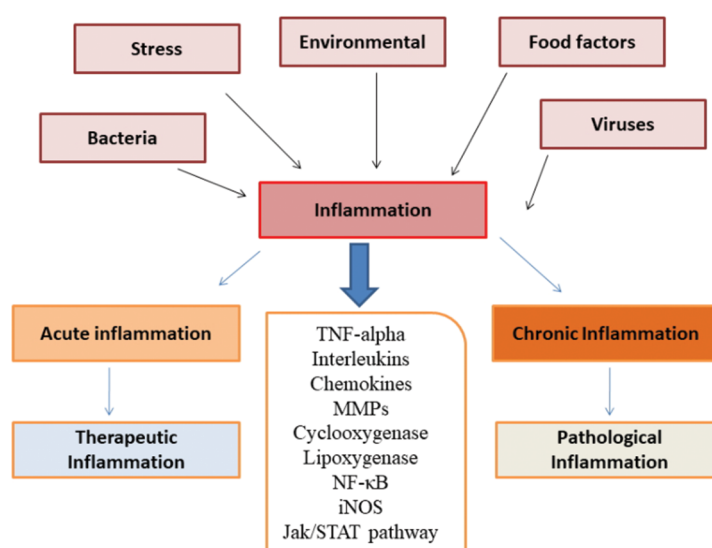
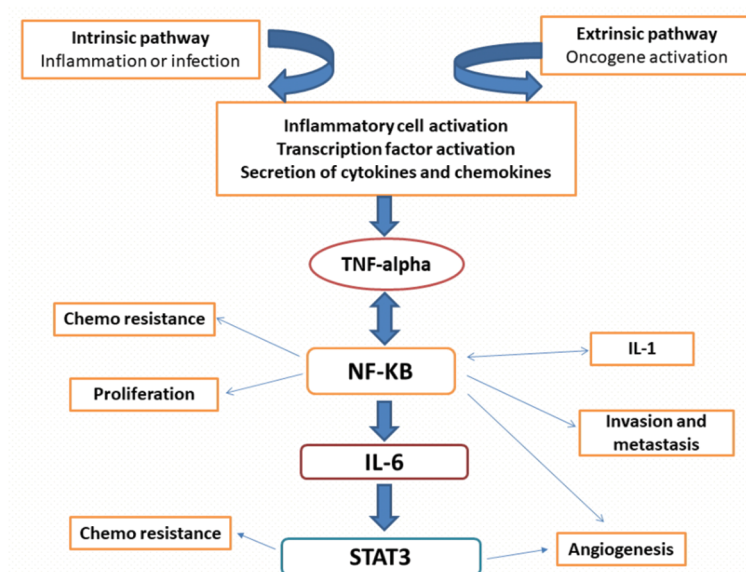


Figure 1. Factors that increase the inflammation, types of inflammation and various receptors involved in inflammation, responsible for activation of tumor cells.

Table 1. Various inflammatory mediators involved in the promotion of different types of cancer^[3,33]

Cancer type	Inflammatory receptor involved
Breast cancer	CXCR4, CCR7, COX-2, MMP1, MM9
Cervical carcinoma	IL-1 α , TNF, COX-1
Ovarian tumors	TNF, IL-8, CXCR4/CXCL12, CXCR4, SDF1, COX-2, iNOS
Glioma	TNF, IL-8, COX-2
Prostate cancer	IL-8, CXCL14, COX-2
Melanoma	IL-8, IL-18, CXCR4, CCR7, CCR10, COX-2
Oesophageal adenocarcinoma	COX-2
Oesophageal SCC and AC	COX-2
Urinary bladder	COX-1, COX-2
Pancreatic carcinoma	IL-1 α , IL-1 β , MIP-3 α , CCR6, COX-2
Head and neck SCC	COX-2
Lung carcinoma	IL-1 α , IL-1 β , COX-2, CXC, CXCL5, and CXCL8
Gastric carcinoma	IL-8, COX-2
Colorectal cancer	IL-6, COX-2
Brain tumors	5-LOX
Colon cancer	IL-6 COX-2, 5LOX, MMP7
Skin cancer	TNF, 5LOX, MMP9
Bladder cancer	IL-6
Renal cell carcinoma	IL-6, CCR3
Leukemia	TNF

**Figure 2.** Various inflammatory targets that provide link between inflammation and cancer by involving in various stages of cancer cell development process.

a death domain (DD) receptor. TNFR2 does not contain the DD domain - its action mediates through TNFR1.^[5] The biological function of TNF executes through activating several signaling pathways like NF- κ B and c-Jun N-terminal kinase (JNK). NF- κ B produces a cell survival signal that produces an anti-apoptosis effect. There are various approaches like transgenic models, gene deletion, and use

of antibodies that have been adopted to check the role of TNF- α in cancer. Data suggest that this receptor has an important role in the development of malignant cells. In the skin cancer study, it was found that TNFR1 mediated signaling activates NF- κ B; which provides signals that help tumor cells to escape from apoptosis.^[6]

Interleukins

Interleukins functioned like intercellular hormones that can alter cellular functions. There are several types of interleukins (IL) that include IL-1, IL-6, IL-8, and IL-18 which play an important role in cancer development. IL-1 α promotes cervical carcinoma and also induces anchorage independence in embryo fibroblasts. IL-1 β also increases the cancer cell growth and is mainly associated with the development of chemoresistance in pancreatic carcinoma.^[7] Production of IL-6 is linked with p53; upon mutation of p53 produce a higher level of IL-6 and mainly involved in the cancers like multiple myeloma, non-Hodgkin's lymphoma, bladder cancer, colorectal cancer, and renal cell carcinoma (RCC).^[8] Cytokine IL-8 has been reported to promote growth and metastasis of a wide variety of tumors. For tumor-associated inflammation, Ras-dependent IL-6 production is required. Expression of IL-8 by human melanoma cells and human ovarian cancer cells correlates with their metastatic potential. IL-8 has been detected in astrocytoma, anaplastic astrocytoma, glioblastomas, and central nervous system cervical carcinoma metastasis.^[9]

Chemokines

The chemokines family has four different members, which, based on the cysteine residues are classified as C, CC, CX3C, and CXC. Chemokines play either beneficial or non-beneficial role for cancer patients. Recruitment of mature dendritic and/or effectors cell provide beneficial effect while chemokine mediated recruitment of immature dendritic cell can increase tumor cell tolerance. In cancer cell development, chemokines play important role in the process like angiogenesis, inflammation, cell migration, etc.^[10] The main role of chemokines in inflammation is to traffic leucocytes to the inflammation site. CC chemokines play an important role in the macrophage and lymphocyte infiltration in melanoma and carcinoma associated with different cancers such as ovary, breast, cervix, and glioma. The concentration of chemokine receptor CXCR4 and CCR7 was found higher in breast cancers. CXC play important role in inflammation, wound healing, cellular cycle regulation, angiogenesis, tumorigenesis, etc. The presence of CXCR4 was found in ovarian cancer while upregulation of CCR4 was found in renal cell carcinoma. CXCR4 activates EGFR in ovarian cancer.^[11]

Matrix metalloproteinases (MMPs)

Matrix metalloproteins are involved in various biological processes like inflammation, wound healing, cellular migration, skeletal formation, and cancer. MMP9 upregulation is found in various stages of tumorigenesis. MMP9 transferred by bone marrow plays a crucial role in skin carcinogens; supported by the evidence that transgenic mice lacking MMP9 have reduced hyperproliferation and invasiveness.^[12] In a breast cancer patient, 70 genes are identified for their poor prognosis; out of those two genes are

MMP-1 and MMP-9. In a recent study, it was found that out of the 95 genes, MMP1 is the second most important gene which has the potential of breast cancer to produce lung metastases.^[13]

Cyclooxygenase (COX)

There are three isoforms of COX that have been identified: A) COX-1 is mainly involved in tissue homeostasis, platelet aggregation, renal blood flow, and maintenance of gastric mucosa, B) COX-2 is found in inflamed and neoplastic tissues, and C) COX-3 is mainly expressed in the brain and spinal cord. The COX pathway by PGH2 synthetase produces PGG₂, which is unstable, and PGH₂ in the presence of PGH₂ synthase and peroxidase enzyme. This converts into various PGs and TxA₂. COX-2 level in cancer can be elevated by cytokines, growth oncogene, and other factors. COX-2 is responsible for the development and growth of a variety of cancers.^[14] The expression of COX-2 is regulated by NF- κ B. In colon carcinoma, the COX enzyme induces angiogenesis in two ways; the first way is modulation of angiogenic factors by COX-2 and COX-1 regulates angiogenesis in endothelial cells.^[15] COX-2 was found at a higher level in epithelial cells of invasive breast cancer. COX-2 also plays an important role in the growth of human lung adenocarcinoma. The physiological effect of PGs and TXA₂ is mediated through G protein-coupled proteinoid receptors which are divided into nine different types. PGE₂ gives biological response through four different receptors; EP1 to EP4. EP4 modulate PGE₂, which is involved in the proliferation of colon cancer cells.^[16] Around 93% of melanomas are expressed with COX-2 with an expression ratio of around 68%. This overexpression plays important role in the development and growth of malignant epithelial cancer cells. In the pathogenesis of oesophageal cancer, involvement of both COX-1 and COX-2 have been detected due to their link with VEGF-A and VEGF-C, which are important modulators of angiogenesis.^[17]

Lipoxygenase

The metabolic process for conversion of arachidonic acid to leukotrienes requires the presence of a 5-lipoxygenase enzyme which is the key factor for this metabolic process. Leukotrienes play important role in some allergic and inflammatory conditions. Apart from that, they are also involved in the pathophysiological functions of the brain like cerebral ischemia, brain edema, and increase the permeability of the blood-brain barrier in brain tumors.^[18] In the nude mice xenograft model treated with colon cancer with cigarette smoke extract, the inhibition of the enzymes COX-2 and 5-LOX reduces the tumor size.^[19] The evidence is further confirmed by the experiment in which cigarettes smoke without filter increases the expression of 5-LOX. This overexpression stimulates MMP and VEGF, which are key factors in the angiogenesis process. 5-LOX inhibitors decrease the colon adenoma formation and also decrease

the expression of VEGF and MMP in tumor cells, ultimately the angiogenesis rate will be decreased.^[20]

NF-κB

Regulation of TNF, COX, LOX, and MMPs is done by the transcription factor NF-κB which is normally present in an inactivated state in most cells, but in cancer cells, NF-κB is found as active. The activation of NF-κB induces inflammation and tumorigenesis.^[21] The activation of the NF-κB response is triggered in the presence of pro-inflammatory cytokines and infectious agents. NF-κB heterodimer is trapped in the cytoplasm when it is bound to IκB, which, upon phosphorylation induces the cytokines, which results in activation of NF-κB. It has been found that in inflammation, the response of NF-κB is triggered through TNF-α which produces anti-apoptosis signals. By enhancing the signaling of NF-κB, cancer cells increase invasiveness. Cancer-associated TNF-α overexpression; inhibition of TNF-α suppresses the response of NF-κB and by this way produces apoptosis process.^[22] In the last few decades, extensive research has been going on NF-κB, and it was found that over-production of this receptor increases the resistance of chemotherapy as well as γ-radiation therapy. Inhibition of NF-κB can sensitize the cancer cells and therefore NF-κB is considered as one of the important targets for the development of chemotherapeutic agents.^[23]

Hypoxia-inducible factor-1 (HIF-1)

Hypoxia-inducible factor contains two subunit alpha and beta; receptor present in the heterodimeric complex. The alpha subunit is less stable as compared to the beta subunit. Recent literature data have shown that inflammation (via inflammatory mediators) can also activate HIF-1 in normoxic conditions.^[24] Various cytokines, hormones can increase the expression of HIF-1. Cytokines such as IL-1β and TNF-α were reported for stimulation of HIF-1α expression. HIF-1α can stimulate the expression of several genes that includes, COX-2, iNOS, vascular endothelial growth factor receptor (VEGF), glucose transporter, etc.^[7] Overactivation of HIF-1α has been demonstrated in various types of cancer as it provides favorable conditions for the development and growth of tumor cells.^[25]

Inducible nitric oxide synthase (iNOS)

There are three different enzymes required for the synthesis of nitric oxide and iNOS is one of them. Cytokines like IL-1β, TNF-α, and IFN-γ can stimulate this enzyme. The expression of iNOS is regulated by transcription factors including NF-κB, activator protein 1, signal transducer and activator of transcription, 1α interferon regulatory protein 1, nuclear factor interleukin-6, and high motility group I (γ) protein.^[26] iNOS mediated cellular changes can produce malignancy, metastasis, angiogenesis of cancer cells which is involved in a variety of cancer types such as

melanoma, prostate, bladder, and colorectal cancer.^[27]

Jak/STAT pathway

STAT family includes seven members, which are involved in different cellular processes like survival, cell proliferation, and angiogenesis. Out of the seven members, the important member involved in cancer is the STAT3 transcription factor. The expression of STAT3 is stimulated mainly by IL6, IL-11, and other members of the cytokine family as well as growth factors. Upon activation, STAT3 phosphorylation followed by homodimerization occurs. This dimer shift into the nucleus binds with DNA and stimulates the transcription of some genes involved in oncogenic activation such as Bcl-2, CDK1, VEGF, etc. Due to this STAT3 is found highly expressed in several cancers like multiple myeloma, leukemia, prostate cancer, lymphoma, breast cancer, squamous cell carcinoma of the head and neck.^[28]

Other pathways

The other pathways which are directly or indirectly activated by inflammation or inflammatory receptors include mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K), CREB signaling pathway, and Wnt/beta-catenin pathway. MAPKs are involved in various cellular processes like cell growth, differentiation, survival, and various immune and stress-related responses.^[29] It is mainly activated and regulated by various cytokines through the phosphorylation process. PI3K is mainly involved in the immune response of cancer cells and is found highly expressed in pancreatic cancer due to mutation of K-Ras in the patient with pancreatic cancer.^[30] CREB plays an important role in cell survival, differentiation of neurons, and metabolism. The process like reverse phosphorylation of serine by various kinase can increase the transcription activity of CREB. The high expression of CREB is found in various types of cancer which includes myeloid leukaemia, non-small cell lung carcinoma, melanoma, mammary carcinoma, etc.^[31] Wnt/beta-catenin pathway is involved in various biological processes like cell polarity, cell proliferation, and cell fate determination during embryonic development and tissue homeostasis. Wnt pathway can interact with many other pathways including HIF-1α, NF-κB, and Notch, stimulate the function of this pathway. Mutation of the Wnt pathway can produce various types of cancer which include cancers of the stomach, liver, intestine, pancreas, and ovaries.^[32]

Role of anti-inflammatory agents in cancer

Targeting inflammatory pathways involved in tumor promotion can be a good strategy for the prevention of cancer, in this regard preventive and anti-cancer effects of anti-inflammatory drugs can be useful (Table 2).

Table 2. Preventive and anti-cancer effects of anti-inflammatory drugs in various types of cancer^[39,46]

Drug	Preventive effect on cancer	Anti-cancer effect
Aspirin	Bladder, breast, colorectal, oesophageal, and lung	Gastric and colon cancer
Celecoxib	Bladder, breast, cervix, colorectal, lung, prostate	Prostate, liver and colon
Ibuprofen	Colon adenoma	Breast cancer
Sulindac	Breast cancer	Colon cancer
Piroxicam	Colorectal cancer	Colon cancer
Dexamethasone	Breast and rectal	Multiple myeloma

Non-steroidal anti-inflammatory drugs

The main role of NSAIDs as anticancer agents is due to their role of inhibition of COX1/2 enzyme which is required for the biosynthesis of prostaglandins and leukotrienes. The level of PGE2 is elevated in different types of cancer production. They increase cancer cell production by favoring angiogenesis, tumor growth, metastasis, and inhibiting apoptosis. PGE2 can activate several cellular pathways like MAPK, PI3K/AKT, and NF- κ B which further activates VEGF, Bcl-2, EGFR, and MMPs and increase the rate of tumorigenesis. The possible mechanism for rational use of aspirin for cancer prevention involved inhibition of various targets like inhibition of COX1/2, certain pro-inflammatory cytokines, modulation on immune response, the effect on PI3K signaling, maintenance of cancer stem cell homeostasis, and decreased glycolytic rate in cancer cells.^[34] The long-term use of NSAIDs may lead to the development of several side effects such as renal failure, GI problems such as acidity, ulcer, and intestinal inflammation which cause perforation and strictures in small and large intestines. This factor can also induce the risk of cancer. To reduce the side effect of NSAIDs, they can combine with 5-LOX inhibitors so that the synthesis of prostaglandins and leukotrienes are blocked.^[35]

The investigation of the link between NSAIDs and cancer was done by Kune et al. The report suggests that patients taking NSAIDs had a significantly lower incidence of cancer. The positive results of NSAIDs in cancer prevention open a new direction in cancer research. The study was done on >1 million subjects with over 30 epidemiological studies; results suggest that NSAIDs can be prototypical agents in the prevention of cancer.^[34,36] Aspirin is a widely used drug in the world whose major role is in cardiovascular diseases. Multiple trials using aspirin for evaluation of anticancer properties have been done; data suggest that aspirin has approximately 20% to 25% ability to reduce incidence and mortality of several types of cancers. The major beneficial effects were found in the stomach, oesophageal and colorectal cancer. Other NSAIDs such as ibuprofen and piroxicam are able to reduce breast and colorectal cancer risk by showing a significant correlation between anti-inflammatory agent use and decreased cancer incidence. The other specific COX-II inhibitors drugs like rofecoxib and valdecoxib are under clinical investigation, but at the

moment, these drugs are used as an adjuvant drugs because of their side effects.^[37-39]

Corticosteroids

Corticosteroids are used as anti-emetic agents to prevent nausea and vomiting driven by cancer chemotherapeutic agents. They are also effective as anti-inflammatory agents in various chronic inflammatory diseases. In the xenograft or experimental model of the breast, colorectal, glioma, and lung cancer. It was observed that pre-treatment with dexamethasone increases the effectiveness of chemotherapy. Dexamethasone was also found to decrease the incidence of lung tumors. The combination of dexamethasone with carfilzomib and lenalidomide had an advantageous effect in multiple myeloma patients.^[40,41]

Statins, metformin, and embelin

Statins are used as anti-hyperlipidemic agents, which are also reported for their anti-inflammatory properties. The mechanism involved in the anti-inflammatory activity is due to the reduction of the pro-inflammatory cytokine, macrophage infiltration, and C-reactive protein. Due to additional anti-inflammatory properties, statins can reduce the risk of several cancers which include colorectal cancer, HCC, and breast cancer.^[42,43] Metformin, a drug used as an oral hypoglycaemic agent, is also reported as reducing the risk for several cancers, including colon, breast, lung, prostate, ovarian, and pancreatic cancers. Its antineoplastic effect is mediated through activation of the AMPK pathway, which counteracts the protumorigenic effect of hyperinsulinemia, the reduction of systemic glucose concentration, which counteracts the Warburg effect and through its anti-inflammatory properties.^[44] Embelin is an isoquinoline derivative reported for its anti-inflammatory properties due to its interference in the arachidonic acid metabolic pathway and can block 5-LOX and PGEs.^[45]

Natural products

Some natural products and foods have anti-inflammatory effects – these include grapes (resveratrol), garlic, and curry powder (curcumin). These compounds have also shown anti-cancer properties due to the induction of apoptosis.

These compounds have anti-inflammatory action due to inhibition of the target NF- κ B, MAPK, JNK, VEGF, and COX and due to this, they have a role in the anticancer activity.^[47] Literature data also suggest that the combination of natural products with chemotherapeutic agents shows beneficial effects. For example, the combination of curcumin with 5-fluorouracil gives synergistic effect while in another study, ginseng saponins were reported to increase the response of cancer cells to chemotherapeutic agents and reduce hematological toxicity after radiation therapy.^[48] Berberine act as an anti-inflammatory agent and also has anti-cancer activity. Activity is due to the inhibition of NF- κ B and COX-2 with IC50 value around 0.3 μ M.^[49]

CONCLUSIONS

Inflammation and inflammatory pathways play important roles in the development and progression of cancer. Inflammation provides the soil for the development of cancer seeds. Targeting inflammation is one of the good strategies for the prevention of cancer. Anti-inflammatory agents have been shown in experimental, clinical, and epidemiological studies. Currently, FDA-approved anti-inflammatory agents have limited use due to a lack of target specificity and toxicity. Changes in dose regimen or combination of an anti-inflammatory agent with other chemotherapeutic agents or development of new anti-inflammatory agents with target specificity and low side effects may provide the solution. The idea of targeting anti-inflammatory pathways to treat cancer is innovative, but at the same time, a better understanding of biochemical pathways and the development of anti-inflammatory agents with more target specificity with fewer side effects need to be more focused on new effective therapeutic strategies.

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Краткий обзор воспалительных биомаркеров, направленных на лечение рака

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Резюме

Воспаление считается общей защитной реакцией локализованной ткани против повреждения, раздражения или отека. Воспаление может быть острым, что является частью защитной реакции; или хроническим, что может привести к развитию различных заболеваний, в том числе рака. Несколько провоспалительных генов играют важную роль в различных клеточных процессах, таких как пролиферация клеток, ангиогенез, метастазирование и подавление апоптоза. Эти провоспалительные гены включают TNF- α , интерлейкины, хемокины, матриксные металлопротеиназы (ММП), циклооксигеназу, липоксигеназу, iNOS, сигнальный путь JAK/STAT и т. д. Все эти гены в основном регулируются фактором транскрипции NF- κ B, который активен во многих типах опухолевых клеток. Поэтому считается, что разработка молекул, нацеленных на провоспалительные гены или фактор транскрипции, является одной из хороших стратегий разработки противораковых агентов. Литературные данные свидетельствуют о том, что многие противовоспалительные средства, в том числе нестероидные противовоспалительные препараты, кортикостероиды, статины, метформин, эмбелин и некоторые натуральные продукты, могут вмешиваться в микроокружение опухоли, ингибируя провоспалительные гены или факторы транскрипции и повышая клеточную активность апоптоза. В этом обзоре описывается связь между воспалением и раком, роль провоспалительных генов и факторов транскрипции в развитии опухолевых клеток и применение противовоспалительных средств при раке.

Ключевые слова

противовоспалительные средства, рак, профилактика рака, воспаление, биомаркеры воспаления
