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REVIEW

The Role of the Mediators of Inflammation in Cancer Development

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Abstract Epigenetic disorders such as point mutations in cellular tumor suppressor genes, DNA methylation and post-translational modifications are needed to transformation of normal cells into cancer cells. These events result in alterations in critical pathways responsible for maintaining the normal cellular homeostasis, triggering to an inflammatory response which can lead the development of cancer. The inflammatory response is a universal defense mechanism activated in response to an injury tissue, of any nature, that involves both innate and adaptive immune responses, through the collective action of a variety of soluble mediators. Many inflammatory signaling pathways are activated in several types of cancer, linking chronic inflammation to tumorigenesis process. Thus, Inflammatory responses play decisive roles at different stages of tumor development, including initiation, promotion, growth, invasion, and metastasis, affecting also the immune surveillance. Immune cells that infiltrate tumors engage in an extensive and dynamic crosstalk with cancer cells, and some of the molecular events that mediate this dialog have been revealed. A range of inflammation mediators, including cytokines, chemokines, free radicals, prostaglandins, growth and transcription factors, microRNAs, and enzymes as, cyclooxygenase and matrix metalloproteinase, collectively acts to create a favorable microenvironment for the development of tumors. In this review are presented the main mediators of the inflammatory response and discussed the likely mechanisms through which, they interact with each other to create a condition favorable to development of cancer.

Keywords Inflammation and cancer · Inflammation mediators · Mechanisms of tumorigenesis

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Abbreviations

AA	Arachidonic acid
AP-1	Activator protein 1
APC	Antigen-presenting cell
cAMP	Cyclic AMP
CCL	Chemokine (C-C motif) ligand
CD	Cluster of differentiation
cHL	Classical Hodgkin lymphoma
CLRs	C-type lectin receptors
COX	Cyclooxygenase
CRC	Colorectal cancer
CXC	Chemokine receptors
DAMPs	Damage-associated molecular patterns
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
FOXP3	Forkhead box P3

GPCRs	G protein-coupled
HPV	Human papillomavirus
ICC	Invasive cervical cancer
IFN	Interferon
IL	Interleukin
MHC	Major histocompatibility complex
miRNAs	MicroRNAs
MM	Multiple myeloma
MMPs	Enzymes matrix metalloproteinase matrix
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK	Natural killer cell
NLRs	NOD-like receptors
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
p53	Tumor protein p53
PAMPs	Pathogen-associated molecular patterns
PGs	Prostaglandins
PRRs	Pattern recognition receptors
PTGER	Prostaglandin receptor
PTGES	Terminal prostaglandin synthase enzyme
PubMed	US National Library of Medicine
RLRs	RIG-like receptors
ROS	Reactive oxygen species
STAT	Signal transducers and activators of transcription
TCR	T Cell Receptor
TGF	Transforming growth factor
Th cells	T helper cells
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
Tregs	Regulatory T cells
Txs	Thromboxanes

Introduction

The primary functions of inflammation are rapidly destroying or isolating the underlying source of the disturbance and then restoring homeostasis so that, being regulated properly, behaves as an adaptive mechanism. One indication of this is the fact that humans with primary genetic defects in the components of inflammation have increased risk of serious infections. A similar phenomenon was observed in animals with defects in genes encoding pro-inflammatory cytokines [1]. Moreover, immunologically relevant genes whose dysfunction leads to spontaneous inflammation are not expressed under normal conditions, suggesting that the inflammatory response is suppressed to maintain health since its deregulation can have devastating effects for the host, resulting in collateral damage and pathology [2]. Thus, despite being a designed response to eliminate pathogens and other agents harmful to the host, the inflammation when deregulated or inappropriately maintained has the potential to cause injury, necrosis, and malignant transformation [3].

Much evidence supports the hypothesis that inflammation participates in providing conditions that lead to cancer. An unresolved inflammation due to any failure in precise control of the immune response can lead to alterations in expression of cancer-related genes and posttranslational modification in cellular proteins involved in the cell cycle, DNA repair, and apoptosis favoring the development of cancer [4]. Currently, it is well established that chronic inflammation is strongly associated with several human cancers, since it leads to the release of pro-inflammatory cytokines, and other immunomodulatory, creating a favorable microenvironment for tumor progression and metastasis [5].

The inflammation generates oxidative stress, which in turn increases inflammation, so that the two are common denominators in carcinogenesis. Oxidative stress generates reactive oxygen species (ROS) that causes DNA damage and activates signaling pathways that deregulate the cell cycle and hence increase the risk of development of cancers. There is a cross-talk between these two mediators, where ROS and inflammation potentiate each other to ultimately cause cancer [6]. Thus, the inflammatory response plays key roles at different stages of tumor development, besides affecting immune surveillance. Immune cells that infiltrate into tumors establish a cross-talk with cancer cells to orchestrate interactions between different mechanisms, which together can lead to the formation of tumors. This review presents a discussion of some mediators of inflammation and the molecular events through which communication is established between immune and tumor cells, as key mechanisms regulating the effects of inflammation and immunity on tumor development.

The literature review was conducted in the electronic databases PubMed (National Institutes of Health), Scopus (Elsevier), and Web of Knowledge (Thomson Reuters), using the following keywords: carcinogenesis, Inflammation and cancer. The databases retrieved hundreds of articles, and we selected those that we thought to be most relevant to our purpose.

Mediators Involved in the Inflammation and Carcinogenesis

The Infections and chronic inflammation contribute to about 1 in 4 of all cancer cases. Mediators of the inflammatory response, such as: cytokines, chemokines, free radicals, prostaglandins, growth factors and enzymes as cyclooxygenase (COX) and matrix metalloproteinase, can induce genetic and epigenetic changes, that result in alterations in critical pathways responsible for maintaining the normal cellular homeostasis and can leading to the development and progression to cancer [7–9].

Cytokines and chemokines are involved in many aspects of growth, differentiation and cell activation. Table 1 summarizes the actions of the main cytokines that play some role in the activation or regulation of the inflammatory response and that contribute in some way to the process of tumorigenesis.

Chemokines are key players of the cancer-related inflammation, whereas their respective receptors and ligands are the downstream genetic events that cause neoplastic transformation and which are abundantly expressed in chronic inflammation, increasing susceptibility to cancer. The components of the chemokine system affect different routes of tumor progression, including leukocyte recruitment, neo-angiogenesis, proliferation, survival, invasion, and metastasis of tumor cells. Preclinical and clinical trials indicate that the intervention in the chemokine system can be a valuable tool for the development of future therapeutic strategies against cancer [35].

It has been shown that the CXCR2 chemokine receptor and its ligands promote angiogenesis and leukocyte infiltration in the tumor microenvironment. In the acidic and hypoxic conditions of the tumor microenvironment, up-regulating the expression of CXCR4 creates a gradient prepared by CXCL12 for migration of tumor-associated fibroblasts (CAF). The axis CXCL12-CXCR4 facilitates metastasis to distant organs and the CCL21-CCR7 chemokine ligand-receptor pair favors metastasis to lymph nodes. These two chemokine ligand-receptor systems are common key mediators of tumor cell metastasis for several malignancies [36].

It has been shown that cancer cells secrete, or induce fibroblasts to secrete the chemokine CCL5, which acts in an autocrine or paracrine manner on tumor cells, which express their receptor (CCR5). This promotes the proliferation of these cells and recruitment of T-reg cells and monocytes to induce activation of osteoclasts and bone metastases, by inducing neoangiogenesis, and to facilitate the spread of tumor cells for distant organs. It is believed that CCL5, produced by cells of classical Hodgkin lymphoma (cHL), may represent an autocrine growth factor of the tumor cells by creating a microenvironment conducive to tumor progression, whereas CCL5 secreted by T cells or fibroblasts may represent a paracrine growth factor. TCD4+ cells expressing CD40L increase the secretion of CCL5 by cHL cells and induce secreting CCL5 by fibroblasts, which promote the recruitment of activated fibroblasts by cHL cells, which in turn recruit T-reg cells, eosinophils, and mast cells [35].

It has been observed that CXCL8, a chemokine of the CXC family, exerts its effects through signaling two G-coupled receptors, CXCR1 and CXCR2 protein. Elevated CXCL8 signaling - CXCR1 / 2 within the tumor microenvironment of various types of human cancers promotes tumor progression through the activation of signaling pathways involved in activation of proliferation, survival, angiogenesis, migration, and cell invasion, through transactivation of the epidermal growth factor receptor (EGFR) [5].

The Role of Transcription Factors NF-κB

The NF-κB family of transcription factors has been recognized as a crucial player in many steps of cancer including initiation and progression, cooperating with multiple other signaling molecules and pathways. This action is mediated by other transcription factors such as STAT3 and p53 or the ETS-related gene ERG, which directly interacts with NF-κB subunits or affects NF-κB target genes. Crosstalk can also occur through different kinases, such as GSK3-β, p38, or PI3K, which modulate NF-κB transcriptional activity or affect upstream signaling pathways. Other classes of molecules that can also act in the integration of these mechanisms involving NF-κB are reactive oxygen species and miRNAs [37].

It is well known that NF-κB regulate the expression of numerous cytokines and adhesion molecules which are critical elements involved in the regulation of immune responses [38]. Furthermore, it coordinates the central signaling pathways of activation of the innate and adaptive immune responses, and that STAT3 regulates the expression of various genes in response to cellular stimuli, playing a key role in cell growth and apoptosis. It has been shown that STAT3 is constitutively activated in many human cancers, including gastric cancer and plays crucial roles in modulating proliferation and survival, cancer cells as well as creating a favorable microenvironment to the formation of metastasis [39].

The activation and interaction between STAT3 and NF-κB have been widely investigated in human cancers such as colon, stomach, and liver cancers. It has been shown that the interaction between these two transcription factors play a vital role in controlling the communication between inflammatory cells and cancerous cells. NF-κB and STAT3 are the main two factors that control the capacity of pre-neoplastic and malignant tumor cells to resist immune surveillance by regulating apoptosis, angiogenesis, and tumor invasion. The understanding of the molecular mechanisms of NF-κB and STAT3 cooperation in cancer development will provide opportunities for the design of new chemo-preventive and chemotherapeutic approaches [40].

The Role of Matrix Metalloproteinase and Cyclooxygenases in the Carcinogenesis

The matrix metalloproteinases (MMPs) are members of the metzincin group of proteases, and constitute a family of zinc-dependent proteolytic enzymes that degrade various components of the extracellular matrix (ECM). Due to their broad spectrum of substrate specificity, MMPs contribute to the homeostasis of many tissues and participate in diverse physiological processes, such as bone remodeling, angiogenesis, wound healing, and immunity. However, the unregulated

Table 1 The role of some cytokines in cancer

Cytokine	Role in cancer development	Ref.
Interleukin-1β (IL-1β)	Supression of p53 expression; Cancerous epithelial cells uses IL-1β as a communication factor instructing stromal fibroblasts, whose expression of p53 was suppressed, creating an inflammatory microenvironment and protumorigenic	[10]
Tumor necrosis factor-α (TNF-α)	Creation of a tumor microenvironment that stimulates the growth and survival of tumor cells through the induction of gene encoding NF-κB dependent antiapoptotic molecules. Furthermore, It cause inflammatory cell infiltration in tumors and promotes angiogenesis, invasion and migration of tumor cell, and suppress cytotoxic T lymphocytes and activated macrophages. TNF-α also contributes to the initiation of tumors through the stimulation of production of genotoxic molecules such as nitric oxide (NO) and ROS, which may cause DNA mutations	[11–13]
Transforming growth factor-β (TGF-β)	TGF-β is essentially an inhibitory cytokine with an anti-inflammatory and immunosuppressive action, and has a central role in the proliferation and function of Treg cells. Changes in its signaling pathways are often observed in human cancer. These alterations attenuate the TGF-β tumor suppressive effects, promoting tumor progression and metastasis. The carcinoma often secrete this cytokine in excess, resulting in increased epithelial-mesenchimal transition with tissue invasion and metastasis.	[14–16]
Interleukin-6 (IL-6)	Stimulation of angiogenesis, promotion of cell proliferation and increased survival of malignant cells, besides inhibit the apoptosis of cancer cells. Clinical studies have shown that high serum levels of IL-6 are associated with advanced stages of various cancers.	[17, 18]
Interleukin-10 (IL-10)	Inhibition of IFN-γ production by Th1 cells as well as production of inflammatory cytokine, including TNF-α, IL-6, and IL-12. Therefore, it is involved in the inhibition of tumor development and progression. However, depending on the context in witch it acts, this cytokine can have action against or favorable to development of tumor. Its presence in the inflammatory microenvironment of the tumor can eliminate the anticancer action of the Th1 response. On the other hand, IL-10 and Tregs also suppress the activity of Th17, which is associated with poor prognosis in several types of cancer.	[19–25]
Interleukin-17 (IL-17)	Induction of many proinflamatory mediators, including TNF-α, IL-1β, and IL-6, suggesting a role in locating and amplifying the inflammation. Besides, several studies have shown large amounts of Th17 cells infiltrated in tumors and high levels of expression of IL-17 in the serum of patients with several types of tumors, suggesting an important role in the tumorigenesis. The Th17/Treg balance was also broken in the peripherical blood of cervical cancer patients.	[26–28]
Interleukin-12 (IL-12)	IL-12 has a protective activity against cancer, acting to prevent initiation, growth, and metastasis of tumors. It stimulates the cytotoxic activity and production of IFN-γ and TNF-α from NK and TCD8 cells, promoting a TH1 immune response, besides an antiangiogenic function. Recently, it has become evident the balance between IL-12 and IL-23 (a promoter of Th17 immune response) is important in the carcinogenesis process.	[29, 30]

Table 1 (continued)

Cytokine	Role in cancer development	Ref.
Interleukin-18 (IL-18)	IL-18 acts in synergy with IL-12 to induces Th1 immune response against cancer. The systemic administration of IL-18 has been chown to have significant antitumor activity in several preclinical animal models. However, its expression and secretion has been observed in several types of immune cells promoting cancer. Its levels has also been elevated in patients with squamous cell carcinoma of the skin.	[31–34]

activity of MMPs leads to pathological conditions such as arthritis, inflammation, and cancer [41, 42].

They are key regulators of ECM and basement membranes, contributing to the development and progression of human malignant tumors due to their interaction with the receptors for growth factors, cytokines, chemokines, cell adhesion molecules, apoptotic ligands, and angiogenic factors [43, 44].

There are several different types of MMPs, including MMP-1, MMP −2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MP-13, and MT1-MMP, which are stimulated and activated by various mechanisms in vascular tissues. Once activated, MMPs degrade ECM proteins and other related signaling molecules, promoting abnormal angiogenesis and remodeling of vascular tissue, and facilitating recruitment of stem / progenitor cells, endothelial cells (ECs), and vascular smooth muscle cells (VSMCs). The changes in the behavior of these cells contribute to the pathogenesis of various disorders [43].

MMPs regulate inflammation by substrate processing of a range of novel substrates including chemokines, growth factors, receptors, binding proteins, proteases, protease inhibitors, and extra-and intracellular multifunctional proteins [45]. MMP-1 and MMP-13 are collagenases that degrade ECM, especially the collagens of type I, II, and III, which are the main components of the interstitial stroma. In colorectal cancer (CRC), the expression of MMP-1 is correlated with a more advanced stage of disease and with poor prognosis. It has been observed that the level of invasion of the lymph nodes by metastasis in CRC were associated with elevated levels of MMP-1. It has been shown that the expression of MMP-13 may be related to tumor biological aggressiveness and used to aid in predicting patient's poor prognosis. In fact, the expression MMP-13 expression was correlated with the decreased survival of patients with CRC [46].

MMP-2 and MMP-9 are gelatinases whose main substrate is type IV collagen and gelatin, but they also have proteolytic activity against other extracellular matrix molecules. Higher levels of expression of these enzymes were found in the plasma of patients with CRC that have metastasis in lymph nodes compared with those without lymph node metastases. MMP-7 is a matrilysin whose expression has been observed in about 80 % of all cases of CRC, and its serum levels are associated with the progression of CRC and decreased survival rate. MMP-7 promotes cancer invasion through cleavage of ECM proteins and activates other MMPs, including proMMP-2 and proMMP-9, to promote invasion of cancer cells. MMP-12 is a metalloelastase expressed predominantly in the macrophage, and it is able to degrade many different substrates and seems to have a protective function in CRC, since its inhibition was considered potentially harmful to the patient with this pathology [44].

On the other hand, the cyclooxygenases are enzymes that convert free arachidonic acid (AA) into prostanoids, including prostaglandins (PGs) and thromboxanes (Txs). There are two isoforms of COX designated, COX-1 and COX-2, being COX-2 the most strongly linked to development and progression of cancer [47, 48]. High expression levels of COX-2 are found in the tissue of colorectal cancer (CRC) and are associated with less survival of patients with CRC [49]. The clinical and epidemiological studies and animal experiments indicate that non-steroidal anti-inflammatory drugs (NSAIDs) are among the most promising chemopreventive agents for this disease. The NSAIDs exert their anti-inflammatory and antitumor effects mainly by inhibiting the action of COX-2, leading to reduced production of prostaglandins [50].

In cells of invasive cervical cancer (ICC), E5, E6, and E7 HPV 16 oncogenes were able to induce the COX/prostaglandin inflammatory axis by increasing the expression of the COX-2 gene [9]. This suggests a direct link between HPV oncogene and activation of an inflammatory response, a potent factor in promoting cancer. Thus, although the initial HPV infection is not associated with inflammation, it is believed that, after integration of the virus into the cell genome, viral persistence occurs, followed by malignant transformation of the infected cell. This occurs due to the activation of inflammatory pathways such as COX-prostaglandin promoting an infiltration of inflammatory and immune cells, creating a favorable microenvironment for tumor progression [51].

Both COX 1 and 2 are significantly represented in cells of ICC, and the products of HPV oncogene and of the PGE2 gene can regulate the expression of the prostaglandin receptor (PTGER) [52]. Furthermore, it was demonstrated that E5 of

the HPV16 protein regulates the expression of PTGER4 in cells of ICC in a way that is dependent on PGE2 production of cyclic AMP (cAMP). This suggests that increased levels of PGE2 on ICC may regulate the function of neoplastic cells in an autocrine or paracrine manner, through the expression of high levels of PTGER2 and PTGER4 prostaglandin receptors [53].

The Role of microRNAs in the Carcinogenesis

MicroRNAs (miRNAs) are small noncoding single-stranded RNAs, which are highly conserved during evolution, and controls the gene expression by degrading the corresponding mRNA, destabilizing and/or inhibition their translation [54]. They have been implicated in the regulation of almost all aspects of cellular functions, including the immune responses, innate and adaptive. miRNAs are involved in many types of inflammatory responses and have a significant impact on the magnitude of the responses. Furthermore, they participate of many regulatory networks of genes whose dysfunctions are associated with human diseases such as cancer [55, 56].

The expression of miRNAs is tightly controlled both spatially and temporally. Although some of them may function as tumor suppressors, the aberrant expression of these molecules has been correlated with various types of human cancers [57]. Besides, several miRNAs are involved in many types of inflammatory response. This is done in two main ways: by affecting development of subpopulations of inflammatory cells such as Th2 and Th17, or by setting the level of immune cell function, e.g., controlling the amount of cytokine produced by DCs [58].

Some miRNAs are expressed in activated T lymphocytes, and each miRNA represses its specific targets, which are often transcription factors specific for a given cell line. This may determines the type of inflammatory T cells produced during inflammation. Specific miRNAs, such as miR-155 and miR-146a, expressed in inflammatory cells, have as targets signaling proteins that regulate the intensity of the inflammatory signal. Ideally, the signaling results in a transient inflammatory response that eliminates the infection without harming the host. The lack of certain miRNAs, such as miR-155, can reduce the magnitude of the immune response, resulting in immunodeficiency. On the other hand, the constant overexpression of miR-155 or deletion of miR-146a can cause a chronic inflammatory condition in which inflammation is not resolved [59].

The expression of miR-21, miR-155, and miR125b is controlled by an undetermined amount of immune signals, the most prominent being TLR, TNF-α, and other cytokines that bind the functions of these miRNAs with inflammatory events [60]. The inflammation modulates the expression of microRNAs that influence the production of several tumor-related messenger RNAs or proteins. These molecular events induced by chronic inflammation contributes to alter important pathways involved in normal cellular function, and hence strengthen the role of inflammation in cancer development [61]. miR-21 is unregulated, both in vitro and in vivo, by oncogenes RAS or SRC, the most frequently activated in human cancers [62].

Among the mechanisms used by miRNAs to promote the initiation and progression of tumors are those that affect the modulation of TLR, cytokines, and their signaling pathways, they also play an important role in the development of cancers associated with infectious agents. The infections with various pathogens induce changes in the expression of miRNAs functionally related to the mounting of the innate immune response. Thus, they are involved in the regulation of the survival and proliferation of immunocompetent cells responsible for the control of infections. The miRNAs miR-21, miR-125, and miR-155 are the most frequently expressed during infection and therefore have a potential role in carcinogenesis induced by infectious agents. It has been shown that overexpression of miR-21 and miR-182 is associated with carcinogenesis associated with HPV with high oncogenic potential [60, 63].

A recent study identified one inflammatory pathway mediated by microRNA that is epigenetically repressed in breast cancers. A high-throughput screen for signal transducer and activator of transcription 3 (STAT3)–regulated microRNAs revealed the microRNA miR-146b as a direct STAT3 target in mammary epithelial cells, but DNA methylation in its promoter area suppressed miR-146b expression in cancer cells. It was observed that deregulated expression of miR-146a and miR-155, facilitates the development of proinflammatory phenotype of Tregs via increased STAT1 activation [64]. Overexpression of miR-146b suppresses NF-kB in an IL-6-dependent manner. The subsequent STAT3 activation decreased invasiveness phenotype in breast cancer cells [65, 66]. It has been proposed that carcinogenesis induced by inflammatory response triggered by miRNA, in colon cancer is related to dysregulation of colon cells and leukocytes, with impact on proteins involved in the PI3K/Atk signaling pathway, thereby contributing to cancer cell proliferation and tumor growth [67].

Conclusions

Chronic inflammation arising of infections or of autoimmune disease precedes development of tumors, suggesting that inflammatory response plays an important role in the tumorigenesis process. Studies show that chronic inflammation can contribute to initiation, promotion, growth, and invasion of tumors, through of oncogenes activation, induction of mutations, loss of the mechanisms of cell cycle control, and of DNA repair, generating a genomic instability which, together

with angiogenesis and tissue remodeling, contributes to development about 1 in 4 cases, of cancer. The mediators of inflammatory response coordinates the central signaling pathways of activation of the innate and adaptive immune responses, and affect various aspects of inflammation, by activating involved genes in survival and proliferation of cells. Also promotes processing the extracellular matrix proteins and other related signaling molecules, causing abnormal angiogenesis and remodeling of vascular tissue, facilitating recruitment and activation or suppression cells of the immune system. Thus, a large variety of inflammatory mediators act together through a complex network of communication through which, they interact with each other's, of synergistic or antagonistic way, to break the cellular homeostasis, creating favorable conditions for initiation, progression and invasion of tumors. Understanding the mechanisms involved in activation, migration and infiltration of immune cells into tumors, as well as the role of a range of mediators of inflammation in the crosstalk of the immune cells with cancer cells, and the molecular events that mediate this dialog, is of great importance to find ways of intervene in this complex network of events, in order of prevent or interrupt the process of tumorigenesis.

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