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Inflammation and cancer: a multifaceted link

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Abstract. – *State of the Art:* **Mounting evidence indicates a link between inflammation and cancer. However, the molecular mechanism(s) remains unclear. Indeed, although preclinical and clinical studies suggest that chronic inflammation can promote cancer development, the role(s) of inflammation in the process is likely very complex and far to be completely understood. Inflammation can promote all stages of tumor development through multiple mechanisms which include enhanced proliferation and resistance to apoptosis of initiated cells, induction of DNA mutations, promotion of angiogenesis, invasion and metastasis. On the other hand, components of tumor microenviroment, including tumor cells themselves, may promote an inflammatory state by producing inflammatory mediators. Moreover, while chronic inflammation might promote tumor formation, acute inflammation might well hamper the process and is indeed used therapeutically to inhibit tumor formation.**

Conclusions: **The present review briefly highlights the relationship between inflammation and tumorigenesis and discusses the possibility to develop chemoprevention and/or therapeutical approaches targeting components of the inflammatory responses.**

Key Words:

Inflammation, Cancer, Tumorigenesis.

Introduction

It was the 1863 when Wirchow[1] for the first time suggested the existence of a link between inflammation and cancer. This hypothesis was based on the observation that inflammatory cells frequently infiltrate tumor stroma. Subsequently, mounting evidence both from preclinical and clinical studies has supported this hypothesis (Table I). However, the question remains still open and the relationship between inflammation and cancer is far to be completely resolved and clarified[2,3]. Inflammation is a tissue's immediate response to noxious stimuli, such as infection, and damage induced by biological, chemical or physical injuries.

Acute inflammation is a short-term response mainly characterized by a leukocytes infiltrate of the damaged tissue, removing of the stimulus and tissue repair. It usually results in healing and the cellular and molecular events involved have been largely identified in the last years as confirmed by the development of several drugs that target them specifically.

Chronic inflammation, on the other hand, is a prolonged and dysregulated response simultaneously characterized by active inflammation, tissue destruction and attempts at tissue repair. It can be the evolution of an acute inflammatory response which fails to eliminate the noxious stimulus but is characterized by peculiar features that makes the two processes completely distinct.

Indeed, the acute neutrophil infiltrate is replaced by macropages and T lymphocytes, the latter being particularly abundant in the case of infection and able to markedly influence the characteristics and the evolution of the inflammatory state based on the class of T cells involved in the process. Undegradable foreign bodies and autoimmune responses, besides persistent pathogens, can also trigger a chronic inflammatory state and lead, sometimes, to the formation of granulomas which represent the final attempt of inflammatory cells to protect tissue from persistent noxious stimuli[4].

Tumor development is a multistep process in which initially normal cell populations undergo a succession of intermediate stages in order to reach a fully malignant phenotype. Each of these intermediate stages is characterized by cells that are more aberrant than those seen in the preceding steps and is as a consequence of new mutations accumulating in the genome of the cell population involved in the process. Thus, tumor development can be considered as a form of Darwinian evolution in which each successive mutation in important cellular genes confers a selec-

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Table I. Evidence supporting a link between cancer and inflammation.

Tumors often arise at sites of chronic inflammation
Inflammatory cells are found in tumors
Chemical mediators that regulate inflammation are present in tumor microenvironment and can be produced by tumor cells
Removal of inflammatory mediators inhibits development of experimental cancers
Long-term use of nonsteroidal anti-inflammatory drugs reduces risk of developing some cancers, especially colon cancer
Signalling pathways involved in inflammation operate downstream of oncogenic mutations

tive advantage to a cell which will undergo a clonal expansion becoming predominant on the surrounding cell populations[5]. It is now clear that cells require multiple mutations to progress to a fully malignant phenotype[6]. These mutations activate oncogenes or inactivate tumor suppressor genes and, given the low mutation rate of mammalian cells, their occurrence span a long period (decades) of an individual life.

Three major phases have been traditionally identified in the process of tumor development: initiation, promotion, and progression[7]. *Initiation* is characterized by irreversible genotoxic event(s) leading to an increased susceptibility of cells to undergo malignant transformation. This will occur in the subsequent *promotion* phase for the survival and clonal expansion of these "initiated" cells under appropriate promoting stimuli. *Progression* is characterized by the progressive acquisition of a fully malignant phenotype leading to the ability to invade surrounding tissues and metastasize. As mentioned, essential to all these three phases is the accumulation of genetic lesions whose occurrence is exposed to multiple influence from the surrounding environment.

Inflammation Can Inhibit Tumorigenesis

Several cell types, such as macrophages, mast cells, dendritic cells (DC) and natural killer (NK) can trigger an inflammatory response by releasing inflammatory mediators upon stimulation by different stimuli. The following acute inflammation aims to the elimination of pathogens and repair of tissue damage. Furthermore, DC and NK cells can also activate the adaptive immune response and, indeed, inflammation often precedes and somehow modulates the quality and strength of the adaptive immune response. Thus, an acute inflammatory response might exert a protective role on tumor development by contributing to tumor surveillance. Moreover, leukocyte infiltrate that characterize acute inflammation might also contribute to destruction of tumor cells. In fact, it was initially believed that leukocytic infiltrates, in and around tumor masses, represented an attempt by the host to eradicate cancer cells and it was demonstrated that artificial infection with inflammation-causing bacteria induced often dramatic regressions of otherwise incurable cancers[8,9]. In addition, infiltration of NK cells in human gastric or colorectal carcinoma has been associated with a favourable prognosis and, on this basis, still today, proinflammatory therapies, such as the use of live Bacille Calmette Guerin (BCG) for local treatment of bladder carcinoma, are used for cancer treatment.

Toll-like receptors (TLRs) represent a family of receptors broadly expressed on hematopoietic and inflammatory cells, particularly phagocytic cells, DCs, and B lymphocytes able to recognize shared structures (patterns) on microbes and pathogens. Activation of TLRs is a key event in triggering an inflammatory response and, although the different receptors share similar signaling pathways, TLRs can induce different inflammatory responses and production of different cytokines. Recent evidence suggests that some members of this receptor family are widely expressed on other cell types including tumor cells. The cellular responses to TLR ligands influence not only production of inflammatory mediators but also other cellular functions, such as differentiation, proliferation and apoptosis. Thus, TLR triggering on tumor cells may result in apoptosis and TLR ligands have been proposed as promising novel therapeutic agents for cancer treatment. TLR activation has been reported to mediate also BCG activity and its antitumor effect is at least in part mediated by the induction of an acute inflammatory reaction at the lesion site. However, the development and suitability of this new class of molecules is still under scrutiny and requires carefully evaluation since, although TLRs triggering on tumor cells may be beneficial, their activation on tumor infiltrating cells may result in tumor promotion, as explained below.

Inflammation Can Promote Tumorigenesis

Despite the observations that an acute inflammatory response might exert a tumor prevention or an antitumor effect, there are no

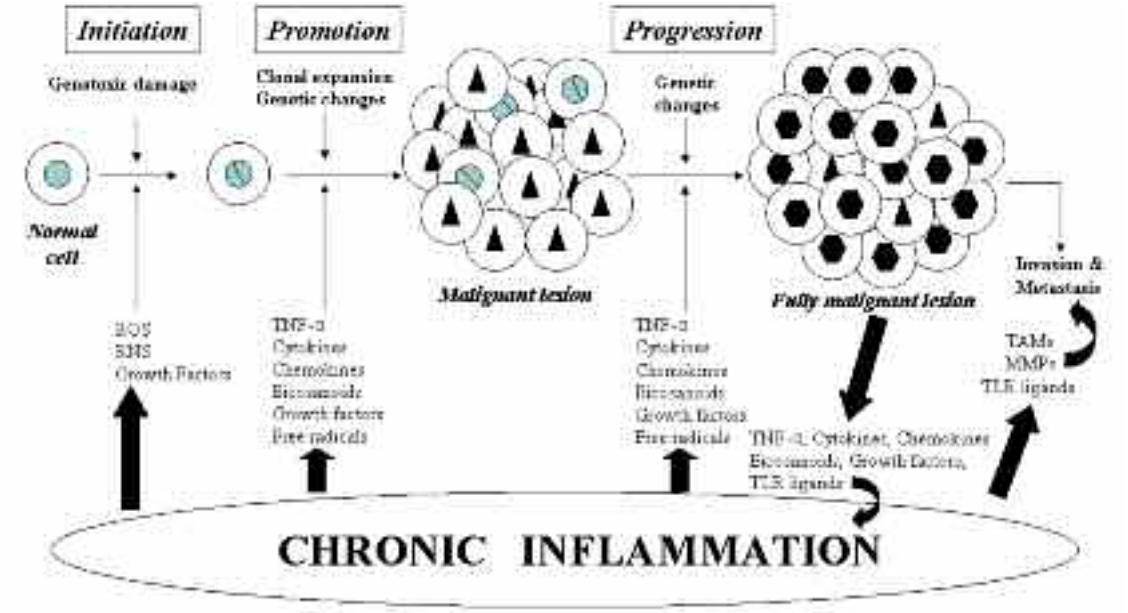

Figure 1. Schematic representation of the complex relationship between chronic inflammation and tumor development. MMP: matrix metalloproteinase; RNS: reactive nitrogen species; ROS: reactive oxygen species; TAM: Tumor-associated macrophages; TLR: Toll-like receptor; TNF-α: Tumour necrosis factor alpha.

doubts that the chronic inflammation can rather promote a tumor development acting at all stages of the process from initiation to progression (Figure 1)[3].

Several types of cancer have been related to chronic infection (Table II) or to chronic inflammatory conditions not associated with pathogens (Table III) and it has been estimated that chronic infection and inflammation contribute to about 25% of all cancer cases worldwide[10].

To understand the link between chronic inflammation and cancer it can be useful to start considering the major features of cancer cells and how they can be related to the inflammatory process. Cancer cells are characterized by six fundamental properties: self-sufficient proliferation, insensitivity to anti-proliferative signals, evasion of apoptosis, unlimited replicative potential, neo-angiogenesis, tissue invasion and metastasis[11]. As previously mentioned, chronic inflammation is simul-

Table II. Major chronic inflammatory states by infectious agents associated with cancers.

Pathologic condition	Associated tumor(s)	Pathogen(s)
Hepatitis	Hepatocellular carcinoma	Hepatitis B and C virus
Gastritis/ulcers	Gastric adenocarcinoma	Helicobacter pylori
Mononucleosis	B-cell non-Hodgkin's and Burkitts lymphoma	Epstein-Barr virus
AIDS	Non-Hodgkin's lymphoma, Kaposi's sarcoma	Human immunodeficiency virus Human herpes virus type 8
Warts	Nonmelanoma skin cancer	Human papillomaviruses (HPV)
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical/anal carcinoma	Neisseria gonorrhoeae, Chlamydia, HPV
Chronic prostatitis	Prostate cancer	Bacteria
Conjunctivitis	Ocular adnexal lymphoma	Chlamydia psittaci
Chronic cholecystitis	Gall-bladder cancer	Bacteria
Opisthorchiasis, Cholangitis	Cholangiosarcoma, colon carcinoma	Opisthorchis viverrini Opisthorchis sinensis
Chronic cystitis	Bladder carcinoma	Schistosoma hematobium

Table III. Chronic inflammatory conditions associated with tumor formation.

Pathologic condition	Associated tumor(s)	Etiologic agent
Sunburned skin	Basal and squamous cell carcinoma (SCC), melanoma	Ultraviolet light
IBD, Crohn's disease, chronic ulcerative colitis	Colorectal carcinoma, small intestine carcinoma	Autoimmunity?
Reflux oesophagitis, Barrett's oesophagus	Oesophageal carcinoma	Gastric acid alcoholism, smoking
Asbestosis, silicosis Bronchitis	Mesothelioma, lung carcinoma	Asbestos fibers, silica smoking
Gingivitis, lichen planus	Oral SCC	Smoking
Liver cirrhosis	Hepatocellular carcinoma	Alcoholism
Chronic pancreatitis	Pancreatic carcinoma	Genetic, alcoholism, smoking
Lichen sclerosus	Vulvar SCC	Unknown
Sialadenitis	Salivary gland carcinoma	Unknown
Chronic cystitis	Bladder carcinoma	Unknown

taneously characterized by active inflammation, tissue destruction and attempts at tissue repair.

The chronic inflammatory state can foster the accumulation of genomic lesions in multiple ways. In fact, one effector mechanism by which inflammatory cells fight microbial pathogens is the production of free radicals such as reactive oxygen (ROS) and nitrogen (RNS) species. These reactive species can induce genotoxic damage, including single and double-strand breaks, DNA–protein crosslinks and modified bases which increase the risk of DNA mutations favouring the appearing of initiated cells[12]. Cells have intrinsic mechanisms to prevent unregulated proliferation or the accumulation of DNA mutations. When DNA damage occurs, cells either repair their DNA and prevent accumulation of mutations or damaged cells will undergo apoptotic cell death. Several pathways that mediate DNA repair, cell cycle arrest, apoptosis and senescence regulate these responses in normal conditions. In an inflamed tissue, damaged cells must be repopulated by the expansion of other cells, often undifferentiated precursor cells such as tissue stem cells. To this aim, an inflammatory microenviroment provides survival and proliferative signals which, in turn, might stimulate survival and proliferation of initiated cells, thereby leading to tumor promotion[9]. The association between inflammation and cancer is clearly demonstrated by several experimental evidence showing that the development of experimental cancers only occurs or is favoured in wounded sites. Indeed, tumor promotion requires not only the survival of initiated cells, but also their expansion and many inflammatory mediators (i.e., cytokines, chemokines, and eicanosoids) are able to promote proliferation of initiated cells and to trigger signal transduction pathways that are implicated in carcinogenesis[13].

Many molecules and pathways, such as the Wnt/β-catenin pathway and the COX-1 and -2 enzymes, have been shown to play a role in both inflammation and tumorigenesis. Another molecule recently involved in the link between inflammation and cancer is NF-κB. Its activation is important in mediating epithelial cell survival in protection from noxious stimuli in intestinal epithelium during an inflammatory response and is equally important in survival and resistance to apoptosis of initiated cells as well as in the promotion of several cancer-related pathways[14,15]. It is noteworthy that NF-κB plays a central role in the production of several inflammatory mediators[15]. One of these key chemical mediators implicated in inflammation-associated cancers is tumour necrosis factor alpha (TNF-α), which is involved in the immune response and in inflammation. This cytokine can be produced by different cell types and its receptor is ubiquitous. TNF-α plays a central role in initiating the inflammatory reactions and is important in its evolution. However, when left unregulated it can cause chronic inflammation and substantial evidence has confirmed that TNF-α is involved in promotion and progression of experimental and human cancers mainly through its ability to activate NF-κB and other transcription factors involved in tumorigenesis[16]. True to its name, high doses of loco-regional TNF-α can cause haemorrhagic necrosis via selective destruction of tumour blood vessels. However, when produced in the tumour microenvironment, TNF-α can act as an endogenous tumor promoter and available data

suggest that its effects on both initiated cells and inflammatory cells in the surrounding stroma are important in promoting the early stages of cancer[2,9,13,14]. Finally, it has to be kept in mind that in some types of viral infection, virally encoded proteins can directly contribute to cellular transformation, as is the case for the E6 and E7 oncoproteins of human papillomaviruses (HPV).

Several cell types take part into the inflammatory response but macrophages are the major players in chronic inflammation being involved in tissue remodelling and repair. Several similarities can be identified between the process of wound repair and tumor development and tumor has been compared to a wound that does not heal[17]. Tumor-associated macrophages (TAMs) are derived from peripheral blood monocytes recruited into the tumor. Upon activation by cancer cells, the TAMs can release the same set of chemical mediators involved in wound repair including growth factors, proteolytic enzymes and cytokines which can affect several aspects of the tumorigenetic process such as: i) invasion and metastasis: macrophages secrete a variety of proteases, such as matrix metalloproteinases (MMPs), urokinase-type plasminogen activator and cathepsin B, able to breakdown the basement membrane and facilitate escape of proliferating tumor cells into the surrounding stromal tissue, thus predisposed to invade surrounding tissue and metastasize; ii) angiogenesis: macrophages cooperate with tumor cells to induce a vascular supply by producing angiogenic factors. This observation has allowed the development of a "biphasic control" model of angiogenesis during tumorigenesis. According with this model, tumor cells would not initially produce by themselves angiogenic growth factors, as they learn to do in the later phases, but would exploit the ability of inflammatory cells (mainly macrophages but also mast cells) to release angiogenic factors; iii) immunosuppression: macrophages secrete factors that suppress the anti-tumor functions of innate immune system. With all these activities, TAMs play an important role in tumor development and the presence of extensive TAM infiltration has been shown to correlate with cancer metastasis and poor prognosis in a variety of human cancers[16,18]. It is noteworthy that most of macrophages activities are triggered by TLRs activation thus complicating the effects that can be obtained using TLR agonists, as previously mentioned.

More recently, TAMs have been also implicated in the epidermal-mesenchymal transition (EMT) of cancer cells. EMT is a process that allows epithelial cells to separate from their neighbors and migrate to distal regions. It plays an important role during embryonic development but also occurs during the process of wound repair when it is induced by macrophage-produced stimuli. TAMs are likely also important in the EMT of epithelial cancer cells during cancer progression thus favouring invasion and metastasis of carcinoma cells[15].

Tumorigenesis Can Promote Inflammation

We have mentioned that pre-malignant tumors are "wound-like", sharing with a healing tissue an inflammatory microenviroment rich in inflammatory cells and chemical mediators, such as growth factors, proteolytic enzymes and cytokines which can, in many ways, stimulate tumor cells proliferation, motility and invasion. However, during later tumor growth, it appears that pro-inflammatory factors come under direct control of tumors themselves. Thus, as previously described for angiogenesis, for which from an initial phase in which tumors cells exploit angiogenic factors released by inflammatory cells follows a phase in which they are directly produced by tumor cells, a similar "biphasic" behavior can be also envisioned for other aspects of cancer-related inflammation. An example is given by eicosanoids which are important inflammatory mediators able to also trigger signal transduction pathways in carcinogenesis. Eicosanoids, and mainly prostaglandins, are produced by COX-2, an enzyme initially expressed at high levels in stromal and inflammatory cells of tumor microenviroment which at later phases is upregulated in cancer cells themselves. The same is true for other pro-inflammatory factors, such as TNF-α, other cytokines and MMPs, which during later tumor growth come under direct control by the tumors themselves. This phenomenon allows tumor cells to develop a self-sufficiency for a "wound-like stroma" which might contribute to cancer-related inflammation and, in turn, favour tumor cells proliferation, invasion and metastasis[19] as confirmed by the observation that TLR activation is required for metastatic growth in an experimental model of lung carcinoma[20].

Conclusion

Inflammation is an extremely complex and fascinating process with a crucial role in a variety of

physiological and pathological processes. It is strictly bound to life and likely appeared with it as cancer did and it is not surprising that the two processes might be linked in some ways. Indeed, a link between cancer and inflammation is supported by epidemiology, histopathology, inflammatory profiles and the efficacy of anti-inflammatory drugs in cancer chemoprevention. An inflammatory microenvironment consisting of infiltrated inflammatory and immune cells and their secreted cytokines, chemokines and growth factors can significantly affect the process of tumor development from the early phases to the final invasive and metastatic stage (Figure 1). However, the relationship between cancer and inflammation is not simple and is far to be completely understood. Unanswered questions include the following: i) is inflammation indispensable for cancer development?; ii) is inflammation sufficient for cancer development?; iii) are there aspects of cancer-related inflammation that are common to all malignancies?. The answer to these questions and the definition of all the causes and mechanisms of chronic inflammation is crucial for our understanding of the link between cancer and inflammation. Moreover, it is essential to explore the possibility to target cancer-related inflammation for the development of innovative approaches for preventing and/or treating cancer[21,22].

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