Inflammation and cancer

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Abstract
There is evidence supporting the hypothesis that inflammation participates in providing conditions that lead to cancer. An unresolved inflammation due to any failure in the precise control of the immune response can continue to perturb the cellular microenvironment, thereby leading to alterations in cancer-related genes and posttranslational modification in crucial cellular proteins involved in the cell cycle, DNA repair and apoptosis. In addition, there are data indicating that inflammatory cells and immunomodulatory mediators present in the tumor microenvironment influence tumor progression and metastasis. Historically, tumor-infiltrating leukocytes have been considered to be manifestations of an intrinsic defence mechanism against developing tumors. However, increasing evidence indicates that leukocyte infiltration can promote tumor phenotypes, such as angiogenesis, growth and invasion. This may be due to inflammatory cells that probably can influence cancer promotion by secreting cytokines, growth factors, chemokines and proteases, which stimulate proliferation and invasiveness of cancer cells. Consequently, events and molecules implicated in this cross talk between the tumor microenvironment and inflammatory process may emerge as attractive targets in anticancer therapeutic interventions with significant clinical impact.

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Key words: Inflammation; Cancer; Cytokines; Proliferation; Cancer progression; Metastasis

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INTRODUCTION
That continuous irritation over long periods of time can lead to cancer was described in Ayurveda (means the science of long life), written as far back as 5000 years ago. Aulus Cornelius Celsus, a Roman medic in the first century, defined inflammation as: “rubor” (redness), “tumor” (swelling), “calor” (heat) and “dolor” (pain). Rodolf Virchow postulated that microinflammation that results from irritation leads to the development of most chronic diseases, including cancer[1]. Although this concept has long been suspected, only recently experimental and clinical studies have confirmed this hypothesis, which is now a generally accepted paradigm[2,3]. It is estimated that underlying infections and inflammatory reactions are linked to 15%-20% of all cancer deaths.

CHRONIC INFLAMMATION AS A PREDISPOSITION TO CANCER
The first evidence that non-cancerous cells might affect the formation and growth of tumors derives from the field of inflammation. Today, there is evidence supporting the hypothesis that inflammation participates in providing conditions that lead to cancer. It is estimated that underlying infections and inflammatory reactions are linked to 25% of all cancer cases. In many epidemi-
logical studies, the role of chronic inflammation in the carcinogenesis process was examined through studies of pro-inflammatory and anti-inflammatory cytokines along with other factors, including viral infections and genetic markers that take part in the inflammatory response. There are well known associations between inflammatory processes and cancer, such as bowel disease (Crohn’s disease and especially ulcerative colitis) and colorectal cancer, viral hepatitis B and C or alcoholic liver cirrhosis and hepatocarcinoma, chronic reflux esophagitis resulting in Barrett’s esophagus and esophageal carcinoma, cervical infection by human papillomavirus and cervical cancer, prostatitis and prostate cancer, pancreaticitis and pancreatic cancer, or gastric infection from Helicobacter pylori, which increases gastric cancer risk by 75%. Tissue injury, whether physical, chemical or infectious, triggers a sequence of events that constitutes the inflammatory response. Inflammation is an important mechanism that can eliminate the agent responsible for the injury and initiate tissue repair by launching a well-coordinated immune response. The inflammatory mechanism involves both innate and adaptive immunity, which is characterized by coordinated blood borne delivery to injured tissues of cells and soluble mediators. After the elimination of the invading pathogen and wound healing, inflammation subsides. However, an unresolved inflammation on account of any failure in the precise control of the immune response can continue to perturb the cellular microenvironment, thereby leading to alterations in cancer-related genes and posttranslational modification in key cell signaling proteins involved in cell cycle, DNA repair and apoptosis. In fact, it is of note that mononuclear inflammatory cells (MICs) are often present at the very early stage of tumor development, in close association with areas of hyperplasia and atypia. These findings support the concept that MICs themselves are a driving force that contributes to tumor initiation and/or initial tumor progression. In addition to macrophages, mast cells and neutrophils can also support tumoral development by leading to upregulation of non-specific pro-inflammatory cytokines, such as interferon-γ, tumor necrosis factor (TNF), interleukin (IL)-1α/β or IL-6. Likewise, activated nuclear factor-κB (NF-κB) transcription factor is one of the main links between inflammation and tumorgenesis and may be key to allowing both preneoplastic and malignant cells to escape from apoptosis. Therefore, all of these factors may act as initiators and promoters of carcinogenesis by directly increasing the proliferation of epithelial cells. Table 1 shows studies reporting the relationship between overexpression of molecular components from inflammation pathway and gastrointestinal carcinogenesis.

On the other hand, it is noteworthy that increased toll-like receptors (TLRs) expression has been described in different human tumors. It is an interesting finding because TLRs are considered a link between innate (non-specific) and adaptive (specific) immunity and contribute to the immune system’s capacity to efficiently combat pathogens. As molecular sensors, TLRs detect pathogen-derived products and couple to different adapter proteins that trigger specific signaling pathways, such as the IL-1 receptor-associated kinase family and serine/threonine-protein kinase (TBK-1). These adapters initiate pathways leading to the activation of their respective transcription factors, NF-κB and interferon regulatory factor 3 (IRF3). Both NF-κB and IRF3 induce the release of various immune and inflammatory cytokines, such as TNF and IL6, which proved to be excellent targets for inflammatory diseases. TLR-deficient mice were found to be protected from or develop less inducible tumors in experimental models. In addition, for example, components of bacteria and viruses have been identified within pathological specimens of men with prostate cancer. There is evidence that the expression of pathogens in the urinary system may contribute to the malignant transformation of prostate epithelia through the activation of TLRs. Therefore, all of this evidence indicates that biological signals elicited from TLR-activated tumor cells might also be a molecular link between inflammation and cancer.

TUMOR MICROENVIRONMENT AND ITS CONTRIBUTION TO TUMOR PROGRESSION TOWARDS METASTASIS

Tumors are composed not only of cancer cells but also of other cell types constituting the stroma. These stromal cells include cancer associated fibroblasts, endothelial cells, pericytes and variable representation of leukocytes. Leukocytes can account for as much 50% of the total tumor mass in invasive breast carcinomas. Initially, tumor cells and cells of the tumor microenvironment respond to tumor hypoxia and necrosis, secondary to excessive tumor cell proliferation, by releasing a number of growth factors and cytokines that are chemoattractive for monocytes and macrophages. These latter factors include colony stimulating factor (CSF)-1, granulocyte-monocyte-CSF, transforming growth factor (TGF)-β and chemokines. In addition, macrophage-tumor cell interaction leads to the release of macrophage-derived cytokines, chemokines and growth/motility factors, such as IL-8 and fibroblast growth factor, which in turn promote the recruitment of additional inflammatory cells.

Historically, tumor-infiltrating leukocytes have been considered to be manifestations of an intrinsic defence mechanism against developing tumors. The presence of leukocytes in tumors was subsequently interpreted as an aborted attempt of the immune system to reject the tumor. However, increasing evidence indicates that leukocyte infiltration can promote tumor phenotypes, such as angiogenesis, growth and invasion. This may be due to inflammatory cells that can probably influence cancer promotion by secreting cytokines, growth factors, chemokines and proteases, which stimulate proliferation and invasiveness of cancer cells. These factors reported...
as released by recruited MICs, included TNF, vascular endothelial growth factor (VEGF)-A and -C, heparocyte growth factor (HGF), epidermal growth factor (EGF) family members, basic fibroblast growth factor, platelet-derived growth factor and chemokines, such as chemokine ligand 12 (CXCL12) and IL-8[31,32,33]. In addition, it is also remarkable that MICs bring in much of the cyclooxygenase-2 (COX-2) present in the tumor environment. It is because COX-2 expression and prostaglandins production within the tumor environment stimulate tumor cell proliferation, survival and motility, but also tumor angiogenesis[36].

CLINICAL RELEVANCE OF INFLAMMATORY COMPONENTS IN TUMOR PROGRESSION

Accumulating clinical data for solid tumors shows a correlation between high-density leukocyte infiltration into tumors and poor outcome of patients with malignancies of different origins, such as breast[17,38], bladder[39], rectum[40], endometrium[41], melanomas[42], gliomas[43] or leiomyosarcomas[44]. In addition, deficient monocyte recruitment at tumor sites in mice lacking CSF-1 expression was shown to attenuate late-stage progression and metastasis formation, suggesting that monocytes contribute to tumor progression[45]. Nevertheless, the presence of inflammatory cells can be a indicator of favorable prognosis in some tumor types, as for example, the presence of macrophages in colorectal cancer[16,47], gastric[48] or ovarian carcinomas[49]. These latter data suggest that, at least in some situations, inflammatory cells may be able to eliminate tumor cells just as they can destroy normal cells. On the other hand, one of the reasons why the prognostic significance of the lymphoid infiltrate at the tumor site remains controversial is perhaps because the evaluation criteria for tumor infiltrates are not sufficiently standardized to yield reliable and reproducible results in different institutions. Leukocyte infiltrate includes a variable representation of leukocytes, including macrophages, neutrophils, mast cells and T and B lymphocytes[31,32]. In addition, there is evidence indicating that different types of leukocyte infiltration occur in different carcinomas and that probably these are induced by different abilities to control tumor growth according to the tumor dissemination[51]. Therefore, inflammatory cells and immunomodulatory mediators present in the tumor microenvironment polarize host immune response toward specific phenotypes impacting tumor progression.

Macrophages are often the most abundant immune cell population in the tumor microenvironment. Recruitment of monocyte precursors circulating in the blood leads to their differentiation into tumor-associated macrophages. It has been reported that, once recruited into tumors, macrophages can assume two different phenotypes: M1 or M2, based on environmental stimuli and each harboring distinct functional properties[52]. The M1 phenotype is associated with inflammation and microbial killing activity, whereas the M2 phenotype is associated with activities which are predominant and key events in cancer, including inhibition of T helper 1 adaptive immunity by immunosuppressive mediators [TGFβ, IL-10 or prostaglandin E2 (PGE2)], production of growth and survival factors (EGF, IL-6 and CXCL8), secretion of angiogenic factors (VEGF, TGFα or PGE2), production of matrix metalloproteases (MMPs) which degrade extracellular matrix, and chemokines able to recruit more inflammatory cells (CCL17, CCL18 or CCL22)[33,32,53].

In this sense, we recently identified a phenotype of

<table>
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<th>Table 1 Overexpression of inflammatory factors in gastrointestinal carcinogenesis</th>
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<tr>
<td><strong>Factors</strong></td>
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<tr>
<td>NF-κB</td>
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<tr>
<td>STAT-3</td>
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<tr>
<td>IL-6</td>
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<td>NOS</td>
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<td>5-LOX</td>
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MICs at the intratumor stroma of 40% of breast carcinomas, which is associated with the development of distant metastasis. These MICs were characterized by overexpression of metalloproteases (MMP)-7, 9, 11, 13 and 14, and tissue inhibitors of metalloproteases (TIMP)-1 and 2[54,55]. This may be because MMPs play an essential role in the degradation of the stromal connective tissue and basement membrane components, which are key elements in tumor invasion and metastasis. MMPs are also able to impact in vivo on tumor cell behavior as a consequence of their capacity to cleave growth factors, cell surface receptors, cell adhesion molecules and chemokines/cytokines[56-58]. Furthermore, by cleaving proapoptotic factors, MMPs produce a more aggressive phenotype via generation of apoptotic resistant cells[59]. MMPs also regulate cancer-related angiogenesis, positively through their ability to mobilize or activate proangiogenic factors[59], and negatively via generation of angiogenesis inhibitors, such as angiotatin and endostatin, cleaved from large protein precursors[60]. In addition, inflammatory cells from tumor stroma play a role in tumor angiogenesis by releasing other factors, such as VEGF, HGF or IL-8, which are able to stimulate and activate endothelial cells. On the other hand, it is now accepted that TIMPs are multifactorial proteins also involved in the induction of proliferation and the inhibition of apoptosis[61,62].

It is noteworthy that many of these molecules which have been identified as playing a critical role in inflammation are regulated by NF-κB. This is a transcription factor that is ubiquitous to all cell types and present in the cytoplasm in its resting stage. There is evidence pointing to the role of NF-κB in tumoral progression. Thus, NF-κB has also been linked with the survival of cancer stem cells[63]. NF-κB regulates the expression of most antiapoptotic gene products associated with the survival of tumors [bcl2-like 1 (bcl-xl), B-cell lymphoma 2 (bcl-2), X-linked inhibitor of apoptosis protein, cellular FLICE-inhibitory protein, inhibitor of apoptosis (IAP)-1 and IAP-2 and survivin], as well as gene products linked with proliferation of tumors (cyclin D1, c-myc and COX-2). In addition, recent data supports a role of the NF-κB-regulated inflammatory network in the progression, diagnosis, prognosis, recurrence and treatment of cancer in patients[64]. Table 2 shows several studies reporting the relationship between NF-κB and/or related molecules with poor prognosis in gastrointestinal tumors.

On the other hand, as mentioned above, elevated TLRs expression has been described in different human tumors[16,24]. It is noteworthy because cancer cells activated by TLR signals may release cytokines and chemokines that in turn may recruit immune cells and stimulate them to release further cytokines and chemokines. This

### Table 2 Different factors associated with poor prognosis in gastrointestinal tumors

<table>
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<tr>
<th>Factors</th>
<th>Gastrointestinal cancers</th>
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<tbody>
<tr>
<td>NF-κB</td>
<td>An independent prognostic indicator of poor outcome in patients with esophageal adenocarcinoma[66]</td>
</tr>
<tr>
<td></td>
<td>High expression of activated nuclear factor-κB indicates poor patient survival in pancreatic cancer[67]</td>
</tr>
<tr>
<td></td>
<td>Activation in hepatocellular carcinoma was implicated in a poor patient outcome[68]</td>
</tr>
<tr>
<td></td>
<td>Associated with a shorter overall survival rate and prognosis biomarker in gastric cancer[69,70]</td>
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<tr>
<td>COX-2</td>
<td>The most important predictor of poor survival in oropharyngeal squamous cell carcinoma[64]</td>
</tr>
<tr>
<td></td>
<td>Correlated with tumor progression and an unfavorable prognostic factor in esophageal carcinomas[60-64]</td>
</tr>
<tr>
<td></td>
<td>Prognostic factor after surgical resection in patients affected by cancer of ampulla of vater[71]</td>
</tr>
<tr>
<td></td>
<td>Associated with liver metastasis and poor survival in primary colorectal cancer[72,73]</td>
</tr>
<tr>
<td></td>
<td>Associated with invasion, metastasis and implicated a poor prognosis in gastric carcinoma[74]</td>
</tr>
<tr>
<td></td>
<td>Linked to an increased risk of hematogenous metastatic spread in rectal carcinoma[75]</td>
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<tr>
<td>CXCR-4</td>
<td>Associated with poor clinical outcome in esophageal cancer patients[76]</td>
</tr>
<tr>
<td>VEGF</td>
<td>Associated with lymph node metastasis and early distant relapse in colorectal cancer[77,78]</td>
</tr>
<tr>
<td>IL-6</td>
<td>An independent prognostic factor for patients with nasopharyngeal carcinoma[79]</td>
</tr>
<tr>
<td>IL-8</td>
<td>Associated with prognosis in squamous cell carcinoma of the esophagus[80]</td>
</tr>
<tr>
<td>MMP-9</td>
<td>VEGF-C and VEGF-D expression was associated with lymphatic metastasis and prognosis in patients with pancreatic adenocarcinoma and induced lymphangiogenesis[81]</td>
</tr>
<tr>
<td></td>
<td>Associated with prognosis in patients with hepatocellular carcinoma[82]</td>
</tr>
<tr>
<td></td>
<td>Associated with prognosis in colorectal cancer patients[83,84]</td>
</tr>
<tr>
<td></td>
<td>Associated with angiogenesis and metastasis in gastric cancer[85]</td>
</tr>
<tr>
<td>NOS</td>
<td>Associated with lymph node metastasis and progression of ampullary carcinoma[86]</td>
</tr>
</tbody>
</table>

**NF-κB**: Nuclear factor-κB; **COX-2**: Cyclooxygenase-2; **CXCR**: Chemokine receptor type 4; **VEGF**: Vascular endothelial growth factor; **IL**: Interleukin; **MMP**: Metalloproteases; **NOS**: Nitric oxide lipoxigenase.
Nevertheless, it is noteworthy that an alternative approach response, has been described in many types of tumors and pathways in the generation of an effective immune response. IL-6 and IL-10, which can interfere with multiple steps of the microenvironment, tumor induce immunosuppression by inefficient, since the tumor itself and the surrounding immune responses against tumor cells is very weak and largely impaired. All of these data suggest that further studies of the expression of TLRs in malignant tumors may help to better understand the process that links inflammation and cancer, as well as to assess the biological and clinical importance of the interaction between tumor and stroma.

**IMMUNOTHERAPY AND ANTI-INFLAMMATORY THERAPY IN CANCER**

It is considered that the main mechanism of tumor immunity is due to an antitumoral T cell response. This antitumor response can be due to the direct killing of tumor cells by CD8 cytotoxic T lymphocytes which recognize major histocompatibility complex class I and other antigens expressed on the surface of tumor cells. However, it is generally assumed that during growth, tumors develop strategies to evade or limit the effects of the host’s immune responses. In most cases, the adaptive immune response against tumor cells is very weak and largely inefficient, since the tumor itself and the surrounding microenvironment tumor induce immunosuppression by the down-regulation of CD8 cytotoxic T lymphocytes response. It has also been suggested that increasing immune activity or immunotherapy will exacerbate the rate of immune escape and select for a tumor sub-population, which will be resistant to immunotherapy. In addition, the secretion of immunosuppressive cytokines and chemokines into the tumor microenvironment, such as TGF-β, IL-6 and IL-10, which can interfere with multiple steps and pathways in the generation of an effective immune response, has been described in many types of tumors. Nevertheless, it is noteworthy that an alternative approach was recently described in which the expression of new, and thereby potent, antigens are induced in tumor cells by inhibiting nonsense-mediated messenger RNA decay (NMD). It has been demonstrated that small interfering RNA-mediated inhibition of NMD in tumor cells led to the expression of new antigenic determinants and their immune-mediated rejection. Therefore, it would be of interest to determine whether the NMD-induced antigens are cross-reactive among different tumors in future studies, and if so, to identify the dominant antigens induced by NMD inhibition.

On the other hand, it is clear that several inflammatory markers are expressed in various cancers and mediate their progression. Consequently, agents which suppress these inflammatory markers or the pathways activated by them have a potential for prevention and treatment of cancer. Some of these agents are being tested, such as steroids (dexamethasone and prednisolone), TNF inhibitors (humira, remicade, enbrel and thalidomide), proteasome inhibitors (velcade) and NF-κB inhibitors (curcumin). It is also of note that most nutraceuticals derived from fruits, vegetables, legumes or spices have been shown to suppress NF-κB activation pathways, thus leading to suppression of various inflammatory markers. COX-2 has also been proposed as a therapeutic target for cancer prevention and treatment [COX-2 inhibitors (COXIB), such as aspirin and celecoxib]. The appearance of cardiovascular complications induced by potent COXIBs has dampened enthusiasm and hampered the widespread use of COXIBs for cancer chemoprevention. TLRs may also represent a good therapeutic target in cancer. In this sense, there are studies that show a variable antineoplastic effect caused by a blockade of TLR3, which activates human plasmacytoid dendritic cells and B cells and this induces potent innate immune responses in preclinical tumor models as well as in patients. The increasing interest in using bindings of nucleic acid-sensing TLR9 as a pharmacological intervention in various diseases is thus understandable. All of these data suggest that further studies of the expression of TLRs in malignant tumors may help to better understand the process that links inflammation and cancer, as well as to assess the biological and clinical importance of the interaction between tumor and stroma.
deoxxygenase. MSCs were able to suppress T-lymphocyte activation and proliferation in vitro\(^{(19)}\). The mechanisms are probably mediated by both direct cell-cell contacts and soluble factors. As regards the effect of MSC on B-lymphocyte function, MSC inhibit immunoglobulin production and arrest B-lymphocytes in the G0/G1 phase of the cell cycle. MSCs have been demonstrated to interfere with dendritic cell differentiation, maturation and function\(^{(98-101)}\). Based on these properties, MSCs are being used in regenerative medicine, for the treatment of autoimmune diseases\(^{(102,103)}\), graft versus host disease\(^{(104-109)}\) and the tropism of MSCs for human gliomas can also be exploited to therapeutic advantage\(^{(110)}\). These cells can be a new alternative in cancer studies; in fact, recently an inhibiting effect of the MSC on the proliferation of the tumor was described\(^{(111)}\).

It seems clear that an understanding of how tumor cells control and benefit from host inflammation responses can open the way towards the identification of therapeutic strategies targeting the molecular mechanisms that underlie relevant tumor-host interactions.

**CONCLUSION**

Chronic and persistent inflammation contributes to cancer development and even predisposes to carcinogenesis. In addition, cellular and molecular components from tumor-associated inflammation may affect neoplastic progression. Events and molecules implicated in this crossstalk between the tumor and inflammatory microenvironment may emerge as attractive targets in anticancer therapeutic intervention with significant clinical impact. Thus, anti-inflammatory agents should be explored for both prevention and treatment of cancer. Their true potential will be recognized only through well-controlled clinical trials.

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