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Review Article

Chronic Inflammation and Cancer: Paradigm on Tumor Progression, Metastasis and Therapeutic Intervention

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Abstract

As early as the 19th century, inflammation has been perceived to have a link with cancer but this perception has waned through the passing of time. In recent years however a renewed interest on inflammation and cancer connection stemming from different lines of work has been evolved that leads to a generally–accepted paradigm. In the tumor microenvironment, smouldering inflammation contributes to the proliferation and survival of malignant cells, angiogenesis, metastasis, subversion of adaptive immunity, reduced response to hormones and chemotherapeutic agents. Thus, this review will try to unravel and explain molecular events, mediators and regulators linking inflammation to cancer.[7]

Key words

Chronic inflammation, Invasion, Metastasis, Chemokines, Cytokines.

الالتهاب المزمن والسرطان . كتصور مبني على تطور الورم والنقائل والتدخل العلاجي

منذ مطلع القرن التاسع عشر تم إدراك أن هناك ارتباطا ما بين الالتهاب والسرطان إلا أن هذا الادراك تلاشى مع مرور الزمن .

الا أنه في السنوات الحالية تم الاهتمام مجدداً بالارتباط بين السرطان والالتهاب، وقد نبع ذلك بناء على الدراسات المختلفة التي ظهرت وأدت الى القبول بشكل عام بهذا التصور .

وفي بيئة الورم المكروية يساهم الالتهاب الخفي الى تكاثر وبقيا الخلايا السرطانية الخبيثة ، التنشؤ الوعائي ، النقائل ، تدمير المناعة التكيفية ، انخفاض الاستجابة للهرمونات والعوامل الكيمائية العلاجية . ولذلك سوف نحاول من خلال هذه المراجعة أن نكشف الغطاء ونشرح الأحداث الجزيئية والوسائط والمنظمات التي تربط الالتهاب بالسرطان . [7]

الكلمات الأساسية :

التهاب مزمن ، غزو ، النقيلة ، كيموكين ، سيتوكين .

Introduction

A link between chronic inflammation and cancer has been suspected since the nineteenth century when Rudolf Virchow first noted that malignant tumors arise at regions of chronic inflammation and contain inflammatory infiltrates.[1–5] Normally, inflammation plays a pivotal role to protect a defined region of infected or damaged tissue by recruiting cells necessary to avoid tissue injury. However, inflammation sometimes fails to subside and this unresolved inflammation can promote tumor cell growth, survival and angiogenesis. Intriguingly, evidence continues to accumulate indicating that unresolved chronic inflammation plays a critical role in the initiation, promotion, malignant conversion, and

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metastasis of several human cancers.[6] Population based studies show that susceptibility to cancer increases when tissues are chronically inflamed; and long term use of non–steroidal anti–inflammatory drugs reduces the risk of several cancers.

Most human tumors are infiltrated by mononuclear cells throughout various stages of their progression. Recently, it became apparent that inflammation can be evoked not only by extrinsic mediators but also by intrinsic mediators. Role of Inflammation in early tumor promotion cancer is caused by defective genome–surveillance and aberrant signal transduction mechanisms.[7] It has been postulated that sustained inflammation at the tumor sites leads to release of soluble factors and reactive oxygen species (ROS), which can contribute to generation of dysplastic changes in genetically altered, initiated tissue cells.[8] These dysplastic tissue cells along with dead cells due to necrosis results in the release of molecules normally stored within cells that act as potent inflammatory mediators, such molecules may be responsible for the triggering of tumor associated inflammation. [9,10] However, the sources of inflammation in tumors that are not associated with a chronic inflammation remain incompletely understood.

Inflammation and Cancer progression

In order to enhance tumor development, infection and inflammation act through signal transduction mechanisms that influence factors involved in either malignant conversion or genomic surveillance. Various types of immune and inflammatory cells are frequently present within tumors. The tumor microenvironment contains admixed population of innate and adaptive immune cells, inflammatory cells in addition to the cancer cells and their surrounding stroma. These diverse cells communicate with each other by means of direct contact or cytokine and chemokine production. It is the expression of various immune mediators and modulators in the tumor microenvironment that dictate in which direction the balance is tipped.[11] There is little genetic evidence that chronic inflammation acts as a direct tumor initiator rather than a tumor promoter. However growing evidences are there that suggest role of chronic inflammation as a tumor promoter.

Tumor inflammatory microenvironment: Pathway, Initiators and its role in Oncogenesis

Cancer and inflammation are linked by two pathways: a) Inflammatory independent pathway, b) Inflammatory dependent pathway. Inflammatory independent pathway is mediated by altered genetic events that leads to neoplasia, which involves activation of proto–oncogenes by mutations, chromosomal rearrangements, gene amplification, and genetic and epigenetic inactivation of tumor suppressor genes. Genetically transformed cancer cells can produce different inflammatory mediators which generate an inflammatory microenvironment in tumors for which there is no underlying inflammatory condition or infection.[1] The inflammation–dependent pathway, on the other hand, is based on underlying infections or chronic inflammatory disease that generates an inflammatory microenvironment rich in cytokines and chemokines that enhance the survival and growth of genetically transformed cancer cells that arise within this environment.[11]

The two pathways converge through the activation of transcription factors such as NF–$\varkappa$B, and hypoxia inducible factor (HIF) 1α in malignant cells.[5] Within the malignant cell these transcription factors control the expression of prosurvival genes, proangiogenic factors, and MMPs.

Role of NF–$\varkappa$B and Hif1αgene in Tumorigenesis

NF–kappaB (NF–kB) proteins are comprise of transcription factors that are involved in the control of a large number of normal cellular processes such as immune and inflammatory responses, cellular growth, and apoptosis. NF–kappaB signalling also has a critical role in cancer development and progression it provides a mechanistic link between inflammation and cancer. It acts as major controlling factor on both pre–neoplastic and malignant cells to resist apoptosis–based tumour–surveillance mechanisms.[5] NF–$\varkappa$B in the inflammatory cells controls the production of cytokines and chemokines that act on the malignant cell as well as the production of proangiogenic factors, such as VEGF.

HIF1α is important for the survival and activation of macrophages and other myeloid cells in the

oxygen–poor environment of primary tumors. NF–κB is also required for full activation of HIF1α through its effect on transcription of the Hif1α gene. [12] The concerted action of these transcription factors and the reciprocal interactions between malignant cells and inflammatory cells are likely to play a key role in formation of the inflammatory microenvironment, typical of advanced tumors.

Role of Reactive Oxygen and Nitrogen Species

Generation of reactive oxygen and nitrogen species (ROS and RNS) by chronic inflammation has been proposed to act as an initiating factor in malignancy through the subsequent DNA damage. [13] There is excessive and prolonged generation of ROS and RNS by resident and infiltrating chronic inflammatory cells, which may increase mutational load[13]. It is mediated by nitric oxide syntheses (iNOS), enzyme involved in free radical generation which is frequently expressed not only in inflamed tissues, but also in premalignant lesions and tumor tissues. [14, 15]

Role of Pro–inflammatory Cytokines in tumor progression

TNF–α, a proinflammatory cytokine role has been demonstrated in tumorogenesis by various cancer models and in chemical skin carcinogenesis. [16,17,18] The absence of TNF–α, or its type I receptor, TNFR1, confers resistance to skin carcinogenesis. [19] TNF–α does not influence the initiation phase of carcinogenesis, however it acts by initiating epidermal induction of TNF–α which in turn serve as a critical mediator of tumor promotion by phorbol esters, which acts via PKCα– and AP–1–dependent intracellular signal transduction pathway in keratinocytes.[16,18] In the absence of TNF–α, the epithelial induction of other cytokines and matrix–degrading proteases that hold out most importance in carcinogenesis and tumor–stroma communication is delayed and/or completely absent.

Chronic Inflammatory Cells and their effects on Tumor and Metastatic progression

Surrounding non–malignant cells such as myeloid and stromal cells population plays a significant role in oncogenic events, thus underscoring the importance of the inflammatory microenvironment in tumorigenesis and metastatogenesis.[3,20] The inflammatory microenvironment of neoplastic tissues is characterized by presence of infiltrating cells of hematopoietic origin, such as leukocytes, macrophages, dendritic cells, mast cells, and T cells. Acute inflammation inhibit malignancy through activation of T and natural killer (NK) cells, and induction of death cytokines such as TNF–α–related apoptosis–inducing ligand (TRAIL), chronic inflammation promotes carcinogenesis through activation of macrophages and mast cells, which produce tumor–promoting cytokines.[3,20,21]

Role of Tumor–associated macrophages (TAMs) in Tumorigenesis and Metastatogenesis:

Macrophages are major component of the inflammatory microenvironment, in oncogenesis they aid in proliferation, invasion and survival of cancer cells through complex pathway mediated by TAMs. Such tumor–associated macrophages (TAMs) can promote tumor development and metastatic progression through multiple mechanisms, including the inhibition of antitumor T–cell–dependent immunity through production of immunosuppressive indoleamine dioxygenase metabolites; inhibition of DC maturation via secretion of IL–10, transforming growth factor (TGF)– β, and M–CSF; as well as attraction of T regulatory (Treg) cells to the tumor.[22]

In addition, TAMs produce numerous cytokines, such as TNF–α, IL–1β, and IL–6; chemokines, such as IL–8, macrophage inflammatory protein (MIP)1, and MIP2; and enzymes that catalyze production of inflammatory mediators, such as cyclooxygenase (COX)–2. All these act to support survival, proliferation, invasiveness, and metastasis of cancer cells. TAMs also secrete matrix metalloproteinases (MMPs) and pro–angiogenic factors, such as vascular endothelial growth factor (VEGF), that stimulate invasion of surrounding tissues and angiogenesis, as well as ROS and RNS, which enhance genomic instability, cell proliferation, and tumor progression.[23,24] The capability to express distinct functional programs in response to different microenvironmental signals is a key feature of macrophages, which is typically manifested during pathological conditions such as infections and cancer.[25,26]

Role of Chemokines in tumorigenesis

Although chemokines have been thought of primarily as leukocyte attractants, and play an important role in the formation of the inflammatory microenvironment. A growing body of evidence indicates that they also contribute to a number of tumor–related processes, such as tumor cell growth, angiogenesis/angiostasis, local invasion, and metastasis.[27] The importance of chemokines in malignant progression was been substantiated by presence of inflammatory infiltrate in absence of immune cells and their functions, thus suggesting that neoplastic cells produce certain chemokines that aid in creating inflammatory microenvironment or induce expression of such factors in nearby host cells.[28] Interestingly, tumor cells use these chemokines not only in creating inflammatory microenvironment but also use them in enhancing tumor growth and survival.[29]

Inflammation and Cancer Invasion and Metastasis

Tumor microenvironment are enriched with inflammatory cells, their mediators and factors such as cytokines, chemokines and enzymes which collectively modulate cancer cell migration, invasion and metastasis.[1–3] Role of inflammation and its mediators in enhancing cancer cells invasion and metastasis is a complex biological process incorporating several inflammatory and pro–inflammatory mediators and factors. Mentioned below are few of the inflammatory mediators and its possible role in invasion and metastasis.

Tumor Necrosis–α as a mediator of invasion and metastasis

Tumor necrosis factor–α (TNF–α) belongs to family of TNF/TNFR cytokine family and plays a role in immunity and inflammation. Recently its role in tumor invasion and metastasis has been acknowledged by evidences that show production of low amounts of TNF–α by malignant and stromal cells within tumors and act as endogenous tumor promoters.[17] TNF–α promotes tumor growth mainly by inhibiting hormonal responsiveness, inducing tissue necrosis and cachexia, thus been found to be associated with poor prognosis. TNF–α also increases vascular permeability and can stimulate the migration, as well as extravasation and intravasation, of cancer cells.[30] It also induces DNA damage and inhibit DNA repair in cancer cells thus facilitating tumor growth.

Role of Interleukins in invasion and metastasis:

The tumor microenvironment consists of tumor, immune, stromal, and inflammatory cells all of which produce cytokines, growth factors, and adhesion molecules that may promote tumor progression and metastases. All intimately interact with one another and play an important role in inflammatory and pro–angiogenic processes and promote tumor cell proliferation.[31] IL–1β a key inflammatory cytokine, also increases tumor growth, invasiveness and metastasis, primarily by promoting angiogenic factor production by stromal cells in the tumor microenvironment.[32,33]

a. Interleukins in tumor growth and metastasis: Ability of IL–1 to induce the expression of angiogenic factors such as VEGF and IL–8 is believed to promote tumor growth and metastasis. Many studies are done on metastatic and non–metastatic cancer cell lines, and these studies indicate that presence of the IL–1RI receptor in cancer cells and IL–1 in the tumor microenvironment are important factors in tumor cell angiogenesis and adhesion and invasion into extracellular matrix.[31,34,35]
b. Interleukins: angiogenesis and loss of hormonal regulation: The ability of IL–1 to promote tumor proliferation and metastases is mediated via neovascularisation; [31] studies suggest the angiogenic effects of IL–1 are indirect. The loss of hormonal regulation of IL–6 has been implicated in the pathogenesis of several chronic diseases,[36] including B–cell malignancies, renal cell carcinoma, and prostate, breast, lung, colon, and ovarian cancers[37] .

Role of Transforming growth factor–β in invasion and metastasis:

TGF–β, a key cytokine exerts potent inhibitory effects on epithelial cell proliferation and also can deter tumor growth.[38] TGF–β produced by cancer cells are subjected to hypoxic and inflammatory

conditions during tumor progression, and is one of major cytokines in tumor microenvironments. It is mediated by induction of *angiopoietinlike4* (ANGPTL4) in cancer cells, which enhances their subsequent retention. Tumor–cell–derived Angptl4 disrupts vascular endothelial cell–cell junctions, increases the permeability of lung capillaries, and facilitates the transendothelial passage of tumor cells.[39]

Thus to set an inflammatory background which promotes tumor progression requires incorporation of large varieties of molecules involved in inflammatory process. Some of these molecular players and their functions to establish link between cancer and inflammation are summarized in Table 1 and Figure 1.

Similarity of Metastatic cells with cells involving in inflammation and wound healing:

Tumorigenesis and metastatic progression share similar features with the process of wound healing.

Molecules	Functions in inflammation	Functions in Cancer
iNOS	Pro–inflammatory cytokines and Downstream of NF–kB.	In tumor microenvironment, induce DNA damage, regulate angiogenesis and metastasis
NF–kB	Promotes and mediate chronic inflammation.	Promotes production of mutagenic reactive oxygen species, protect transformed cell from apoptosis, inducing pro inflammatory cytokines
HIF–1α	Promotes chronic inflammation	Enhance the glycolytic activity of cancer cells, Contribute to angiogenesis, tumor invasion, and metastasis by transactivating VEGF.
COX–2	Produce inflammation mediator prostaglandins	Promote cell proliferation, antiapoptotic activity, angiogenesis, and metastasis
IL–6	Inflammatory and pro–angiogenic process mediator	Promote tumor growth
TNF– α	Mediates chronic inflammation.	Induce DNA damage and inhibit DNA repair, Promote tumor growth, Induce angiogenic factors and neovascularisation in cancer cells.
Chemokines	Mediates inflammation.	Facilitate invasion and metastasis by directing tumor cell migration and promoting basement membrane degradation

Table 1: Molecules and their links between cancer and inflammation

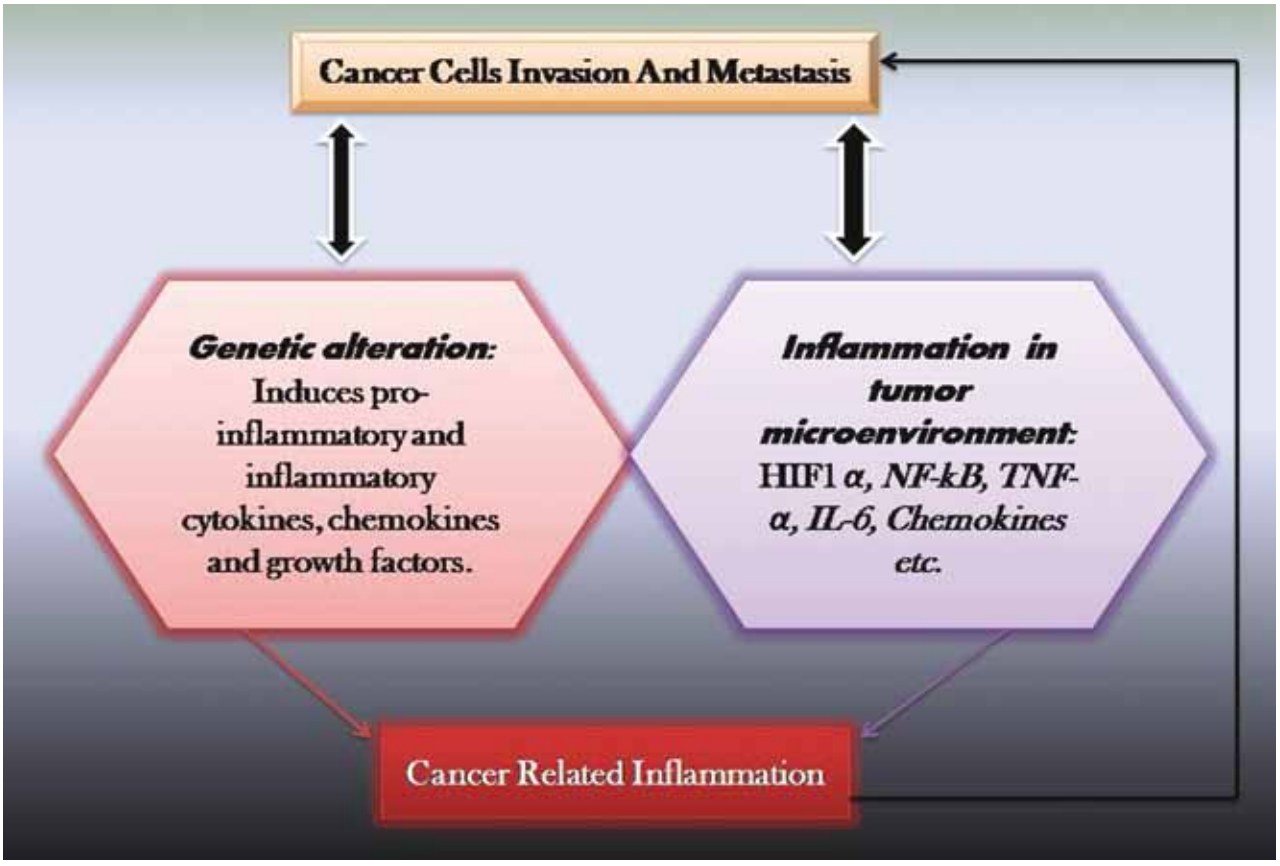

Figure 1: Link between cancer and inflammation: Genetically altered cancer cells may produce different inflammatory mediators, generating inflammatory microenvironments in tumors and promoting tumor progression and metastasis.

As established for the neoangiogenic process that accompanies wound healing secrete vascular permeability factors such as VEGF. The same sequence of events (angiogenesis) found in tumors also occurs during wound healing and in a range of chronic inflammatory diseases. However, the molecular alterations that allow tumors to behave like wounds that do not heal.[40]

Genetic basis of Inflammation and Cancer Metastasis

Inflammatory cytokines, chemokines, and the proinflammatory microenvironment also have a role in shaping the gene expression profile that is required for metastatic behavior of cancer cells. Ectopic expression of Twist, a key transcription factor in metastasis results in loss of E–cadherin– mediated cell–cell adhesion, activation of mesenchymal markers, and gain of motility by malignant cells.[41] Several studies are done on metastatic breast cancer and findings suggested that Twist can contribute to invasion and metastasis by promoting the EMT developmental program. Indirectly it may also be induced by inflammatory microenvironment in response to NF– $\varkappa$B activation and therefore can be upregulated in reaction to inflammation.[42] This provides a mechanism through which tumor–associated inflammation may stimulate metastatic progression through induction of Twist–dependent EMT. Apart from Twist various other molecules which aid in metastatic progression are IKKα by repressing transcription of anti–metastatic gene maspin.[43] Repression of maspin expression required nuclear translocation of catalytically active IKKα.

Therapeutic intervention of anti–inflammatory drugs against Cancer progression and metastasis

Through the evidences of various studies and expression of inflammatory mediators and regulators in various neoplasms, it is a well–established fact that persistent chronic inflammation in tumor microenvironment stimulates tumorigenesis and metastatic progression. Henceforth therapies directed against inflammation and its mediators or preventing

their recruitment onto tumor microenvironment will reduce risk of cancer progression and metastasis. Use of nonsteroidal anti–inflammatory drugs (NSAIDs) such as aspirin, flubiprofen etc. were found to reduce risk of cancer as well as have antimetastatic effect through its ability to inhibit COX–1, 2 and also by inhibiting platelet aggregation.[44] Unfortunately, some of the current NSAIDs, especially those that are COX–2 selective, exert side effects such as life–threatening stomach ulcers, heart attacks, and strokes in a considerable number of patients which limits their utility.

Conclusion

The role of chronic inflammation on cancer progression and metastasis is a complex biological process involving pro–inflammatory, inflammatory mediators and regulators. Such inflammatory tumor microenvironment may facilitate angiogenesis and promote the growth, invasion, and metastasis of tumor cells. Thus far, research regarding inflammation–associated cancer development has focused on cytokines and chemokines as well as their downstream targets in linking inflammation and cancer. Moreover, other proteins with extensive roles in inflammation and cancer are also proposed to be promising targets for future studies. The continuing study of the molecular mechanisms that lead to inflammatory cell activation within tumors and to tumor growth, angiogenesis, and progression should help in the identification of new therapeutic targets and aid in the design of new drugs. Thus understanding of such inflammation induced tumorigenesis may also aid in the development of vaccines and other strategies to enhance antitumor immunity.

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