Advances in research on the interaction between inflammation and cancer

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Abstract

Inflammation is the body’s response to cell damage. Cancer is a general term that describes all malignant tumours. There are no confirmed data on cancer-related inflammation, but some research suggests that up to 50% of cancers may be linked to inflammation, which has led to the concept of ‘cancer-associated inflammation’. Although some cancer patients do not appear to have a chronic inflammatory background, there might be inflammatory cell infiltration in their cancer tissues. The continuation of the inflammatory response plays an important role in the initiation, promotion, malignant transformation, invasion and metastasis of cancer. Anti-inflammatory therapy has been shown to have some effects on the prevention and treatment of cancer, which supports a pathogenic relationship between inflammation and cancer. This review describes the interaction between inflammation and tumour development and the main mechanism of regulation of the inflammatory response during tumour development.

Keywords
Inflammation, cancer, prostatitis, prostate cancer, metastasis, microenvironment

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Introduction

Inflammation exists in the processes of many diseases. In addition, inflammation may play an important role in the occurrence and development of cancer.\(^1\) In fact, many kinds of malignant tumours, such as renal cancer, prostate cancer, gastric cancer and skin cancer, appear to occur at the site of inflammation or infection.\(^2,3\)

Inflammation and tumour development

Inflammation and tumour promotion

Many malignant tumours such as renal cancer, lung cancer, prostate cancer and sarcoma first occur at the site of inflammation or infection, which suggests that persistent infection can lead to chronic inflammation; and that the inflammatory environment can increase the probability of mutation and accelerate the mutation of cells.\(^4-7\)

The upregulation of peroxisome proliferator activated receptor \(\delta\) in gastric progenitor cells may be one of the causes of gastric cancer.\(^8\) Interleukin (IL)-6 trans-signal transduction induces the occurrence of epidermal growth factor receptor (EGF-R)-related tumours such as lung cancer by affecting the activity of EGF-R.\(^9\) In prostate cancer, the occurrence of inflammation is considered to be the significant factor for malignant transformation.\(^10\) In the ‘injury and regeneration’ model, prostate tissue is infiltrated by inflammatory cells that release active substances that have also been linked to bacterial and viral infections, increased uric acid and consumption of prostate carcinogens.\(^11\) In addition to these mechanisms, the release of active substances can also promote the growth of inflammatory contraction.\(^12\) Shrivelled cells may exhibit the characteristics of stem cells, genetic free radical damage, increased risk of mutations and chromosomal abnormalities that eventually lead to tumour formation and development.\(^13\) Over the past 10 years, the association between inflammation and cancer has been well studied and confirmed at the epidemiological, clinical and molecular levels.\(^14\)

Activated inflammatory cells such as neutrophils and macrophages release oxides that promote DNA damage in proliferating cells, producing reactive oxygen species (ROS) and reactive nitrogen species.\(^13\) Inflammation-induced mutations can lead to inactivation and inhibition of the dislocation repair gene, and ROS can also be inactivated by direct oxidation of the dislocation repair enzyme.\(^15\) Therefore, various mutations in the cells accumulate in succession, resulting in oncogene activation and inactivation of tumour suppressor genes.\(^16\) Sustained stimulation of chronic inflammation can cause immune tolerance in the body and mutant cells cannot be identified and cleared in time.\(^17\) The combination of the above factors ultimately leads to the inevitable occurrence of tumours.\(^1\) For example, sodium dextran sulphate (DSS) can cause the development of chronic inflammation, causing DNA damage, which in turn causes colonic epithelial cell tumours.\(^18\)

Inflammatory cells produce growth factors and cytokines that activate downstream nuclear factor kappa-light-chain-enhancer of activated B cells (NF-\(\kappa\)B), activator protein-1, signal transducer and activator of transcription (STAT) and mothers against decapentaplegic (SMAD) transcription factors, and caspase proteins to produce tumour-promoting factors that induce cell proliferation and survival factor production, which promotes the development of tumours and the growth and survival of tumour cells.\(^19\)

Tumour induction is the process by which a single tumour cell grows into a fully developed primary tumour. The growth of the initial cells depends on both the promotion
of cell proliferation and the reduction of cell death, both of which can be stimulated by inflammation.\textsuperscript{20} Inflammatory reactions can produce some targeted chemical factors and cytokines that promote tumour development, which can play a role in paracrine and autocrine ways to ensure that inflammatory cells are actively recruited in the tumour microenvironment.\textsuperscript{20}

The growth of tumours requires an ever-increasing supply of blood vessels in the tumour.\textsuperscript{21} Vascular inflammation promotes tumour progression.\textsuperscript{21} In addition, tumour-associated macrophages can also promote tumour angiogenesis, induce hypoxia signals and produce chemical factors and proangiogenic factors.\textsuperscript{22}

Most tumour-promoting transcription factors work through multiple effectors and are regulated by multiple transcription factors, which have different levels of importance in different cell types. For example, NF-κB and STAT3 can activate several inflammatory target genes (such as COX2, iNOS and TNFA), promote the expression of antiapoptotic proteins (such as B-cell lymphoma-2 [Bcl-2] and B-cell lymphoma-extra large [Bcl-XL]) and cyclins (including cyclin D1, D2 and B).\textsuperscript{23–25} In addition, overexpression of cyclooxygenase-2 (COX-2) can oxidize and damage DNA, and increase carcinogenic products.\textsuperscript{26} Moreover, overexpression of COX-2 can also reduce the antiproliferation and apoptosis of tumours, as well as the antiangiogenesis and immune surveillance activity of endothelial cells and myeloid cells, thus promoting tumour growth and creating favourable conditions for the development of distant metastases.\textsuperscript{26–28} Nicotinamide adenine dinucleotide phosphate oxidase, a product of oxidative stress, can aggravate genomic instability and increase the risk of carcinogenesis.\textsuperscript{29–31} These inflammatory target genes can also promote cell-to-cell contact and increase cytotoxicity and death through bystander effects.\textsuperscript{32} They can also exhibit another potential tumour-inducing mechanism that interferes with p53 synthesis and reduces p53-mediated gene surveillance.\textsuperscript{32} Using the classical model of mouse colitis-associated cancer DSS/azoxymethane, research has demonstrated that tumour-promoting cytokines are mainly derived from inflammatory cells, and that NF-κB inactivation in myeloid cells can inhibit tumour growth.\textsuperscript{33} Inhibition of inflammation may reduce the risk of colon cancer.\textsuperscript{33} IL-23 is also a tumour-promoting factor that is expressed in most tumour-associated macrophages in a manner that relies primarily on STAT3 and NF-κB.\textsuperscript{34}

**Inflammation and tumour metastasis**

Tumour metastasis mainly refers to tumour cells that invade the lymphatic vessels, blood vessels or other passages from the primary site and are transported to other tissues where they continue to grow, forming the same type of tumour as that at the primary site. Recent research has clearly shown that tumour metastasis is achieved by the interaction of tumour cells, immune cells, inflammatory cells and interstitial components.\textsuperscript{35} It is a complex and ongoing process. First, the tumour cells invade the epithelium. Inflammation participates in the process of tumour metastasis through the blood by affecting the function of vascular basal cells.\textsuperscript{35}

Tumour metastasis is associated with a variety of inflammation-related proteins (such as proteolytic enzymes);\textsuperscript{36} and inflammatory cells can also produce transcription factors (such as NF-κB and STAT3) and corresponding gene products (such as IL-6, IL-1, cell adhesion molecules, COX-2).\textsuperscript{37} For example, inflammatory factors such as IL-1 and IL-6 can promote the expression of matrix metalloproteinases through NF-κB and STAT3, thereby inducing invasion and metastasis of tumour cells, and providing an explanation for the role of inflammation in cancer.\textsuperscript{38} The transfer of
cancer cells requires many proteins that control the expression of epithelial–mesenchymal transition regulators. Inflammatory cells are an important source of proteases that hydrolyse components of the extracellular matrix. Transforming growth factor-β (TGF-β) is an anti-inflammatory cytokine induced by tumour cells, myeloid cells and T-lymphocytes, which activates the SMAD transcription factor and mitogen-activated protein kinase pathway protein.

In the development of early metastatic lesions in polyomavirus middle T-antigen-induced breast cancer, macrophages appear in areas where the basement membrane is destroyed and systemic consumption of macrophages leads to a reduction in lung metastasis. Tumour-associated macrophages (TAMs) produce a variety of growth factors and cytokines, which in turn stimulate tumour cell growth, exercise and invasion. This effect is mainly mediated by tumour necrosis factor-α (TNF-α) secreted by macrophages, because the neutralization of TNF-α by anti-TNF-α antibodies significantly inhibits macrophage-mediated tumour cell invasion.

Fibroblasts are one of the main components of the tumour stroma. These cancer-associated fibroblasts (CAFs) have much in common with activated fibroblasts and can accelerate tumour progression. Research has shown that CAFs play a main role in the invasion and migration of tumour cells. CAFs increase the levels of IL-6 and enhance tumour cell invasion. A study that used myofibroblasts isolated from surgically resected colon cancer specimens found that myofibroblasts stimulated the invasive growth of breast and colon cancer cells. In addition, CAFs can cause destruction of vascular structures in pancreatic ductal adenocarcinoma, which will create obstacles to drug administration.

Myeloid-derived suppressor cells (MDSCs) are present in many cancer patients. MDSCs can be activated by a variety of factors such as vascular endothelial growth factor (VEGF) and IL-6, most of which are related to inflammation. In turn, the activated MDSCs can further produce pro-inflammatory factors, leading to an amplification of the pro-inflammatory response. By regulating the production of cytokines, MDSCs not only inhibit the acquisition of immune responses, but also regulate the natural immune response, thus directly promoting metastasis. Research has shown that the levels of MDSCs is closely related to metastatic tumour burden and response to chemotherapy. MDSCs in breast cancer can accelerate tumour metastasis and invasion.

**Cancer-related inflammation and tumour microenvironment**

**Tumour microenvironment**

The tumour microenvironment (TME) is the internal environment in which tumour cells proliferative and live; and it includes the tumour cells and various fibroblasts and neighbouring cells. Microvessels, intercellular substances and biomolecules infiltrate into the area. Tumours attenuate antitumour immune responses via the TME, maintain proliferation, escape apoptosis, maintain an inflammatory environment and promote angiogenesis. Shifting immune surveillance from tumour removal to tumour induction is a complex process involving multiple signalling pathways that involve tumour cells and other non-tumour cells such as CAFs. The tumour-promoting immnosuppressive process of cancer immune surveillance relies on the recruitment of CAFs, TAMs, tumour-associated neutrophils and bone marrow-derived inhibition. Regulatory T (T_{reg}) cells and other cells change the balance of immune cells in the TME. The end result is increased inflammation and angiogenesis,
as well as the conversion of the neutrophil phenotype from N1 to N2, the conversion of macrophages from M1 to M2, and the conversion of T-lymphocytes from Th1 to Th2, as well as cytotoxic lymphocytes and antigen-presenting cells. The dramatic reduction in the number of mature dendritic cells allows more monocyte precursors to be used to support the growing population of TAM2 and MDSCs. Subsequently, the network of cytokines established between these immune cells enhances each other and helps maintain the number of immune cells in the tumour-promoting TME. In addition, it seems that TGF-β, VEGF, hypoxia-inducible factor-1α, chemokines and inflammatory cytokines (especially Th2) are induced. Cytokines are associated with tumour-induced angiogenesis, inflammation and immunosuppression. In CAFs, this relationship seems to be supported by regulatory B cells, IL-4, IL-6, IL-10 and TGF-β, which are maintained by the mutual enhancement of Th2, TAM2, TAN2, T_reg cells and MDSCs.

**The role of proinflammatory cytokines in the tumour microenvironment**

Immune cells, cancer cells and stromal cells form a complex regulatory network in the TME. They interact with each other by inducing each other, regulating receptors and exerting biological functions. Immunostimulation and immunosuppression often occur in cancer and various cytokines such as macrophage migration inhibitory factor, TNF-α, IL-6, IL-10, IL-18 and TGF-β upregulate inflammation into cancer. In particular, some cytokines activate the NF-κB and STAT family of transcription factors, which in turn link the inflammatory environment, tumours and immune cells with other components of the tumour ‘secreting proteome’ and directly control TME by regulating survival factors. Taking IL-6 as an example, its effect is similar to that of a growth factor and it has a direct effect on the TME. Currently known IL-6 dependent tumours include breast cancer and lung cancer. IL-6 upregulates the expression of VEGF and promotes angiogenesis. VEGF regulates the balance between T_reg and Th17 cells by promoting the induction and survival of Th17 cells.

The effects of proinflammatory and pro-neoplastic cytokine secretions exceed those of immunoregulatory cytokines such as TGF-β and IL-10. IL-6 also activates bone marrow cells, including macrophages and neutrophils, to stimulate their phenotypic differentiation. In addition, expression of IL-6-dependent chemokine (CC motif) ligand 20 on cervical fibroblasts promotes the proliferation of Th17 to maintain long-term tumorigenicity. The expression of STAT3 acts downstream of all cytokines in the IL-6 family and is extensively involved in tumorigenesis. The IL-6/STAT3 pathway activates gene expression of antiapoptotic proteins and proliferating proteins, such as Bcl-2, Bcl-XL and myeloid cell leukemia-1 in epithelial cells and cancer cells, which enhances the antiapoptotic ability of tumours. Clinically, IL-6 expression levels are closely related to tumour stage, metastasis and prognosis. Patients with high levels of plasma IL-6 often have late-stage tumours with distant metastases, and their prognosis is worse than for patients with lower levels. Thus, pro-inflammatory cytokines are key regulators of the TME, controlling tumour cell proliferation, promoting inflammation and tumour metastasis. Furthermore, research has shown that networks of proinflammatory cytokines IL-1β, IL-11, IL-18, IL-17 and TNF-α are key regulators of the TME, which can control tumour cell proliferation and promote inflammation, angiogenesis and tumour metastasis.
Relationship between NF-κB and inflammation-related cancer

NF-κB promotes cancer

NF-κB plays an important role in the development of cancer. For example, abnormal activation of NF-κB can be detected in different types of cancer cells, which is associated with tumour recurrence and poor prognosis.68

The programmed cell death of defective cells involves the process of apoptosis, which promotes the development of cancer and the tolerance of cancer cells to radiation and chemotherapy.69 Selective deletion of the \( \text{IKK}_\beta \) gene in intestinal cells can reduce the incidence of colon cancer by 80% without affecting the size of the tumour formation, suggesting that the signal from NF-κB that is dependent on \( \text{IKK}_\beta \) in intestinal cells mainly affects the tumour initiation stage, but has no effect on tumour progression.69 Deletion of the anti-apoptotic gene \( \text{Bcl-XL} \) might have an effect on the apoptosis of intestinal cells. However, when the deletion of \( \text{IKK}_\beta \) occurred in intestinal cells, the incidence of colon cancer was reduced.69 These results indicate that the NF-κB-mediated pathway can promote the development of two different cell-specific behaviours: NF-κB promotes the expression of anti-apoptotic proteins in intestinal cells to inhibit the programmed death of precancerous cells, while NF-κB in bone marrow cells promotes the production of cytokines to promote the growth of precancerous cells.70,71

Antagonism by the IL-6 receptor can inhibit IL-6-induced signalling, thereby inhibiting tumour growth.70 NF-κB promotes the development of liver cancer mainly by inhibiting precancerous lesions.72 Peripheral endothelial cells and inflammatory cells participate in the activation of NF-κB.72 NF-κB may regulate the release of a variety of cytokines and affect reduction/oxidation reactions, thus it appears to participate in tumour inflammation and affect the prognosis of tumour patients.72 There is also evidence that cytokines such as TGF-β, IL-4 and IL-13 can affect the TME, regulate apoptosis and affect angiogenesis.73–75 In addition, these inflammatory factors may regulate the NF-κB pathway and the activity of immune cells, which may affect the prognosis of the tumour.76,77

The anticancer effect of NF-κB

Recent studies have found that NF-κB also has an inhibitory effect on tumour development. For example, blocking NF-κB entry into the nucleus by overexpression of \( \text{IkB}_\alpha \) promotes the invasive growth of epithelial cells induced by oncogene Ras, similar to squamous cell carcinoma.78 The mechanism responsible for this phenomenon remains unclear. It is thought that it might be due to the regulation of NF-κB by the oncogene-induced cell aging process and the inactivation of NF-κB leads to the malignant transformation of these cells.79

In a mouse model of liver cancer induced by the carcinogen diethylnitrosamine (DEN), DEN induced hepatocyte death and initiated a compensatory proliferation process, which caused liver fibrosis that eventually develops into liver cancer.80 It has been found that the expression of \( \text{IKK}_\beta \) and \( p38_\alpha \) in hepatocytes can inhibit this effect of DEN, prevent liver fibrosis and liver cancer, and its specific loss will increase the carcinogenic rate of DEN.80 Similarly, the specific loss of \( \text{IKK}_\gamma \) or IKK-activated kinase TAK1 in hepatocytes can also cause spontaneous liver injury, ROS accumulation, hepatocyte death, liver fibrosis and liver cancer.80 Reduced expression of \( \text{IKK}_\alpha \) or gene mutations cause a decrease in the histological differentiation of squamous cell carcinoma and a poor prognosis.80 In a study of the carcinogenic effects of chemicals in mice, it was found
that the decrease in the expression of IKKα leads to an increase in the number of Ras-induced skin tumours, a larger volume and a promotion of skin cancer development. According to the above results, IKKα appears to be a tumour suppressor gene, but its specific mechanism remains unclear. It is speculated that this may be independent of the kinase activity of IKKα. It can itself act as a transcription factor into the nucleus, regulating and inhibiting growth, differentiation and migration. In the nucleosome, IKKα interacts with histone H3 to competitively inhibit the binding of histone methyltransferase SUV39h1 to H3.

Conclusion

Inflammation can affect all aspects of tumorigenesis and progression as well as various stages of cancer treatment. The interaction between different cytokines induces functional changes in immune cells and tumour cells, forming a dynamic and complex tumour immune microenvironment.

Declaration of conflicting interest

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