Review

Interplay between inflammation and cancer

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A B S T R A C T

Tumor-promoting inflammation is one of the hallmarks of cancer. It has been shown that cancer development is strongly influenced by both chronic and acute inflammation process. Progress in research on inflammation revealed a connection between inflammatory processes and neoplastic transformation, the progression of tumour, and the development of metastases and recurrences. Moreover, the tumour invasive procedures (both surgery and biopsy) affect the remaining tumour cells by increasing their survival, proliferation and migration. One of the concepts explaining this phenomena is an induction of a wound healing response. While in normal tissue it is necessary for tissue repair, in tumour tissue, induction of adaptive and innate immune response related to wound healing, stimulates tumour cell survival, angiogenesis and extravasation of circulating tumour cells. It has become evident that certain types of immune response and immune cells can promote tumour progression more than others. In this review, we focus on current knowledge on carcinogenesis and promotion of cancer growth induced by inflammatory processes.

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1. Introduction

The process of inflammation was first connected with cancer in 1828 by French surgeon – Jean Nicholas Marjolin. Marjolin observed the development of squamous cell carcinoma near a burn scar, although he described it as an ulcer. Similar observations were made by an English surgeon Caesar Hawkins who in 1833 described cases of skin cancer developing near burn wounds years after the injury. Thirty years later, Rudolf Virchow noted that leucocytes are present in cancerous tissue, and named chronic inflammation as one of several conditions predisposing to cancer development. Virchow suggested, that carcinogenesis is related to “lymphoreticular infiltration” in the inflamed tissue and that further spread of “infection” (dissemination of cancer cells) relies on tumour’s vascularisation.

Current knowledge and most recent reports show that there is a direct causal link between inflammation and carcinogenesis. Currently, it is estimated that up to 20% of cancer-related deaths are linked with inflammatory reaction. The risk of developing cancer is increased by chronic inflammatory diseases (for example, hepatitis and liver cancer), chronic infections or inflammations caused by environmental exposures like asbestos or cigarette smoke. Additionally, administration of non-steroidal, anti-inflammatory drugs is connected with a lower risk of developing various tumours and decreased mortality further underlining the role of inflammation in neoplastic transformation. In 2011 tumour-promoting inflammation was named by Hanahan and Weinberg as an enabling characteristic among other hallmarks of cancer. Although inflammation is an essential pro-tumorigenic factor, it is also often present in the microenvironment of cancers which do not manifest inflammatory origins. Mantovani divided cancer-related inflammation into two pathways: the intrinsic pathway connected with genetic events causing inflammation and neoplastic transformation, and the extrinsic pathway which describes the inflammatory conditions...
promoting carcinogenesis. Further research of pathways underlying these processes might improve treatment and diagnosis of inflammation-related cancer. In this review, we focus on current knowledge on carcinogenesis and promotion of cancer growth induced by inflammatory processes (Fig. 1).

1.1. Reactive oxygen species and reactive nitrogen species in carcinogenesis

Carcinogenesis is a complicated process that can be divided into three phases: initiation, promotion, and progression. Initiation is possible due to the acquisition of a primary mutation in a cell, which enhances cellular growth. In the promotion stage, the cells undergo clonal divisions. However, genetic and epigenetic changes are also present. Progression involves the transformation of promoted cells into highly malignant derivatives. One of the mechanisms through which inflammation induces carcinogenesis is through the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Various inflammatory cells, like activated neutrophils and macrophages, are capable of producing ROS and RNS through activation of oxidant-generating enzymes like NADPH oxidase, xanthine oxidase, inducible nitric oxide synthase (iNOS) and myeloperoxidase (MPO). These oxidants can cause damage to nucleic acids, proteins, and lipids, and are produced to kill bacteria and parasites which induced inflammation in the first place. However, the induction of damage to DNA can result in mutagenesis and further neoplastic transformation. Researchers found that fibroblasts exposed in vitro to activated human neutrophils undergo transformation and that these cells could form benign or malignant tumours after injection to mice. Neutrophils were capable of transforming cells through production of reactive oxygen intermediate. However, it is essential to note that activated neutrophils are also capable of oxidizing polycyclic carbohydrates, making them a DNA alkylating agent. Production of ROS can lead to the induction of oxidative DNA damage, like the production of 8-oxy-7,8-dihydro-2′-deoxyguanosine (8-oxy-dG) which leads to G:C to A:T transversion frequently present in human cancers. 8-oxy-dG has been utilized as a marker of oxidative damage to DNA (41). Another important factor in inflammation-induced mutagenesis is the production of nitric oxide (NO) which is synthesized by NO synthases. During inflammatory processes expression of iNOS is induced in many inflammatory cells, particularly macrophages and neutrophils, in response to the presence of bacterial products. NO can react with superoxide (O$_2^-$) forming peroxynitrite (ONOO$^-$), which is less stable than NO, however, causes much more damage to the DNA. Peroxynitrite causes the production of 8-oxy-dG and 8-nitroguanidine which leads to transitions and transversions of nucleic acid bases. Additionally, NO has been shown to induce deamination of nucleic acid bases, and inactivation of DNA damage repair proteins. Although the association between NO and increased cancer risk has been observed before, the direct causal link was first demonstrated in the C3H 10T1/2 fibroblasts, which presented a reduced number of transformed foci after NOS inhibitor treatment.

Currently, inflammation and nitric oxide are both implicated in the origins of various cancers, most notably gastrointestinal (GI) cancers. The role of NO in GI cancers is observed in clinical data – the presence of iNOS is observed in over 50% of patients with colorectal carcinoma, and there is a correlation between a higher expression of iNOS and decreased survival and incidence of lymph node metastasis. However, the relationship between GI cancers and iNOS is not entirely understood. Although there is a correlation between iNOS expression in tumour and the patient outcome, a recent study by Norton et al. showed that increased iNOS expression in tumour infiltrating macrophages correlates with favorable patient outcome. Nitric oxide has also been implicated in gastric cancer. Infection with *Helicobacter pylori* is one of the leading factors predisposing to gastric cancer. *H. pylori* activate inflammatory genes in gastric epithelium which activate the NFκB pathway which, in turn, increases expression of iNOS.

Additionally, the infection with *H. pylori* induces a response from macrophages which produce NO to eliminate the infection. Gastric mucosa of patients with gastric cancer presents higher levels of iNOS in patients positive for *H. pylori*, than in negative patients. *H. pylori* are strongly associated with inflammation-induced gastric cancer, and studies are linking epigenetic alterations with this process.

Another important factor in inflammation-induced carcinogenesis is the role of epigenetic changes. The term epigenetic changes describes alterations in DNA methylation, chromatin configuration, histone modifications, and control of noncoding RNA. These epigenetic changes can result in the silencing of tumour-suppressor genes, which is an essential factor in tumorigenesis. Chronic inflammation can induce epigenetic changes in the inflamed tissue through changes in the metabolism caused by activated immune cells, and through the induction of DNA-damage critical to the activation of epigenetic changes. A higher incidence of CDH1 (a tumour suppressor gene), promoter methylation in gastric mucosa, is observed in dyspeptic patients and patients with gastric cancer associated with *H. pylori*. Increased methylation of promoters of tumour suppressor genes was also observed in patients with Barrett’s esophagus, an inflammatory condition predisposing to the development of oesophageal cancer.

1.2. Prostaglandins in carcinogenesis

Another factor contributing to the inflammation-induced carcinogenesis are prostaglandins. Prostaglandins are produced from arachidonic acid by cyclooxygenases (COX), and are widely present in inflammatory response – their synthesis is significantly increased in the inflamed region. Non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin inhibit the production of prostanoids
by COX enzymes, showing the importance of these factors in the promotion of pain, inflammation, and fever.\textsuperscript{29} Two isoforms of COX have been described – constitutively expressed COX-1 and inducible COX-2, the latter playing an important role in carcinogenesis. COX-2 is synthesized by inflammatory macrophages and monocytes. However, it can also be produced in fibroblasts, epithelial cells, and endothelial cells.\textsuperscript{5}

Interestingly, prostaglandins are also directly connected with ROS and RNS – peroxynitrite, a highly reactive product of the reaction between nitric oxide and superoxide, can also stimulate the production of COX-2.\textsuperscript{30} Studies on animal models and epidemiologic observations show that treatment with NSAIDs lowers the risk of developing GI cancers, especially colorectal cancer.\textsuperscript{31}

Additionally, COX-2 specific inhibitors present even more pronounced capacity to inhibit colon carcinogenesis than conventional NSAIDs.\textsuperscript{32} COX-2 can induce production of angiogenic factors in colon cancer cells, potentially contributing to the development of new blood vessels stimulating the growth of tumour.\textsuperscript{33} Stimulatory role of COX-2 is not limited to colon cancer, increased expression of this gene has also been observed in lung cancer, prostate cancer, and breast cancer.\textsuperscript{34} The mechanism between COX-2 expression and colorectal cancer is not yet clear; there is some hypothesis aiming to explain that. COX-2 plays an essential role in the production of prostaglandin E2 (PGE2), which interacts with EP receptors.\textsuperscript{35} EP2 receptor subtype is known to act as tumour promoter – mice with EP2 receptor knockout have a significantly lower risk of developing lung, skin, and breast tumours after induction of carcinogenesis.\textsuperscript{35} EP2 promotes carcinogenesis predominantly through activation of angiogenesis-related to induction of VEGF. However, it also regulates motility and survival in endothelial cells, which also governs angiogenesis.\textsuperscript{36,37} EP4 is another receptor with well-described connection to tumorigenesis. The PGE2-induced activation of EP4 receptor results in the development of pro-tumorigenic immune response.\textsuperscript{38}

EP4 receptor pathway has been implicated in the activation of Treg cells which inhibit the inflammatory response to the tumour.\textsuperscript{39} Inhibition of the EP4 signaling reduces the risk of developing metastasis of breast cancer in the mouse model.\textsuperscript{39} This effect was related to the inhibition of the function and migratory ability of Natural Killer (NK) cells through EP2 and EP4 signaling.\textsuperscript{39}

Additionally, recent reports show that PGE2 signaling through the EP4 receptor can promote growth and invasiveness of tumour cells.\textsuperscript{40} The research of the role of COX-2 in the development of cancer, especially of the colon, has advanced significantly in recent years. Inhibition of COX-2 could present a viable tool for prophylaxis and treatment of inflammation-induced tumours.

1.3. Cytokines in carcinogenesis

During inflammation, cytokines are synthesized by immune and stromal cells by cell-to-cell signaling. Cytokines regulate the inflammatory response; however, during chronic inflammation, some cytokines can contribute to carcinogenesis. In chronically inflamed tissue, tumour cells are exposed to inflammatory cytokines, and some tumour cells acquire the ability to respond to these signals giving them a growth advantage. There are several cytokines which are involved in chronic inflammation and also play an important role in tumorigenesis and progression of cancer. TGF-β is an immunosuppressive cytokine released during an injury to prevent uncontrolled progression of inflammation. TGF-β is also present in the tumours microenvironment, and cancer cells can utilize it for progression.\textsuperscript{41} Tumour-related TGF-β can originate from different sources – cancer cells themselves, stromal cells, and inflammatory cells infiltrating the tumour.\textsuperscript{42} This cytokine mediates its effects through binding with type II receptor (TGFBRII), which contains a cytoplasmic serine/threonine kinase domain.\textsuperscript{43} Mutations in TGFBRII gene are often present in malignancies with microsatellite instability, allowing cancer cells to avoid the suppressive effect of TGF-β. TGF-β is responsible not only for the suppression of immune reaction but can also regulate processes related to cancer progression, like epithelial–mesenchymal transition (EMT). Initiation of the EMT process in cancer cells increases the mobility and ability to invade, which contributes to the processes of tumour invasion, dissemination, and development of metastasis.\textsuperscript{44} TGF-β signaling axis has been identified as a strong inducer of EMT process in hepatocellular carcinoma.\textsuperscript{45} Research conducted by Cohen et al. have shown that activated human T cells secrete inflammatory factors, including tumour necrosis factor (TNF-α), interleukin (IL)-6 and TGF-β were able to induce EMT in inflammatory breast cancer.\textsuperscript{46} TGF-β plays an important role in the local invasion. However, clinical data shows that it also contributes to the promotion of distal metastasis. Dalal et al. observed that the increased level of TGF-β is present in a great majority of metastases of infiltrating duct carcinoma of the breast.\textsuperscript{47} Research shows that TGF-β takes part in two processes crucial for the development of distal metastasis: priming of tumour cells and colonization of the new metastatic niche. In the primary ER- breast tumour, TGF-β induces angiopoietin-like 4 (ANGPTL4) in cancer cells, which facilitates disruption of cell-to-cell junctions in lung capillaries, increasing their permeability and allowing lung seeding of cancer cells.\textsuperscript{48} Production of TGF-β also supports the growth of cancer cells in the metastatic niche. TGF-β induces production of osteolytic cytokines by cancer cells which stimulate bone cells to produce factors promoting the growth of tumour cells.\textsuperscript{49} The most important of the osteolytic factors induced by TGF-β, parathyroid hormone-related protein (PTHrP), induces differentiation of osteoclasts and bone resorption, and inhibition of this factor reduced bone metastasis in a mice model.\textsuperscript{50} The extensive role that TGF-β plays in tumour growth and progression could make it a viable target for cancer therapy.

TNF-α is a pro-inflammatory cytokine involved in chronic inflammation, apoptosis, tumour growth, invasion, and angiogenesis.\textsuperscript{51} Although first described as a cytokine with anti-tumour activity, current data shows that the activity of TNF-α can promote carcinogenesis.\textsuperscript{52} TNF-α exerts its effects through activation of receptors TNFR1 and TNFR2.\textsuperscript{53} While TNFR1 is expressed in every cell type in the organism, except erythrocytes, the TNFR2 is expressed exclusively on immune cells. High levels of TNF-α have been found in the serum of cancer patients with the active disease either as a response to cancer or as a part of the carcinogenic process.\textsuperscript{54} The role of TNF-α in carcinogenesis has been confirmed using murine cancer models. Mice with induced knock-out of TNF-α receptor – TNFR1 – are resistant to the development of chemically-induced skin cancer and liver cancer.\textsuperscript{55,56} Ji et al. used a mice model to show that TNF-α promotes lymphangiogenesis both in vitro and in vivo, and also promotes lymphatic metastasis.\textsuperscript{57} TNF-α-related promotion of tumour development and metastatic progression depend in large part on NF-kB signaling.\textsuperscript{58,59} Pikarsky and colleagues\textsuperscript{59} showed that in hepatocellular carcinoma mouse model inhibition of NF-kB through anti-TNF-α treatment induced apoptosis in transformed hepatocytes and prevented progression into hepatocellular carcinoma. NF-kB has been implicated in carcinogenesis of gastrointestinal cancers (reviewed in \textsuperscript{60}). On the molecular level, activation of NF-kB induces expression of genes responsible for processes connected with cancer progression, like angiogenesis, invasion, EMT, and metastasis.\textsuperscript{51,62} In vitro research by Dong et al. showed that chronic exposure of HeLa cells to TGF-β followed by TNF-α leads to NF-kB-dependent induction of EMT and cancer stem-like phenotype which strongly correlate with more aggressive cancers.\textsuperscript{63}
Although TGF-β and TNF-α are often investigated in the context of inflammation-induced carcinogenesis, evidence exists implying that other cytokines also contribute to this process. Macrophages infiltrating the tumour are responsible for the production of several inflammatory cytokines. In cutaneous melanoma, the infiltration of macrophages correlates with the invasion of primary melanomas. Additionally, two inflammatory cytokines produced by activated macrophages, TNF-α and IL-1α, stimulate the production of interleukin-8 (IL-8), vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in melanoma cells.64 All three of these cytokines stimulate angiogenesis in melanoma, contributing to better vascularization of the tumour. IL-6 is another well-characterised pro-tumorigenic cytokine, which can be present in different stages of cancer development from promotion to metastasis.65 Increased level on IL-6 in blood correlates with a higher risk of developing colorectal cancer and overall poor prognosis.66,67 IL-6 has been shown to stimulate growth and proliferation of colorectal cancer cells as a consequence of TGF-β signaling in tumour infiltrating T lymphocytes.68 These results were confirmed in both a mice model and patient tumour samples. Authors also suggested that targeting the IL-6 signaling might be used in the therapy of colon cancer.

1.4. Inflammation and senescence

Secretion of inflammatory molecules is also linked to the senescent cells. The term cellular senescence describes the arrest of cell cycle, induced in order to decrease the risk of cancer development from ageing cells. The phenomenon was first described by Hayflick and Moorhead, where primary in vitro cells showed a limited number of possible cell divisions.69 Senescence can be induced by various factors, like telomere shortening, oxidative stress, DNA damage, activation of oncogenes (oncogene-induced senescence, OIS) or administration of chemotherapy or ionizing radiation therapy (therapy-induced senescence, TIS).70,71 Induction of senescent phenotype in pre-malignant cells is recognised as one of the mechanisms by which the organism restricts tumour progression.72 Malignant tumour cells are not capable of undergoing senescence at the same rate as the cells of premalignant lesions. Senescent cells are characterised by their distinct phenotype, expression of marker proteins (for example senescence-associated β-galactosidase) and production of molecules which transmit inflammatory signals. This inflammatory phenotype of senescent cells is termed senescence-associated secretory phenotype (SASP). Secretion of specific factors allows the senescent cells to modify the microenvironment. Coppe and colleagues divided these factors into categories: soluble signaling factors, proteases and insoluble extracellular matrix components.73 Additionally, the authors noticed, that secreted proteases (like matrix metalloproteinases and serine proteases) present three major activities: shedding of membrane-associated proteins, degradation of signaling molecules, and degradation of extracellular matrix. Kullman et al. showed that IL-6, which can be produced by senescent cells, plays an important role in cell-cycle arrest and activation of oncogene-induced senescence.74 Authors also theorized that this cytokine can act pro-oncogenically in some situations (stimulation of advanced melanoma) and anti-oncogenically in others (induction of OIS in early-stage neoplastic cells). Other factors associated with the SASP include IL-1, chemokines (CXCL and CCL), and proteins related to the IGF pathways.75

1.5. Inflammation in cancer recurrence

Inflammation can not only lead to the induction of neoplastic transformation or promotion of tumour growth but can also play an important role in the process of recurrence after therapy. Surgical excision of breast cancer is a standard in therapy; however, surgical intervention elicits an inflammatory response which may impact the growth of cancer cells.76 These observations were confirmed in animal models. Following the excision of the primary tumour in mice, the serum of the animals was enriched in growth factors which stimulated the proliferation of cancer cells.77 This hypothesis has also been tested using surgical wound fluids collected from breast cancer patients after breast-conserving therapy.77 Surgical wound fluids induced proliferation, migration, and invasiveness of cancer cells in vitro.

Interestingly, this effect was abrogated by administration of intraoperative radiotherapy, showing, that the choice of therapy might significantly impact the wound healing and inflammatory response following surgery. The same group also showed that inflammation after surgery could promote stemness and tumour-initiating properties in breast cancer cells through STAT3 signaling.78 The composition of surgical wound fluids was also investigated, and authors showed that the concentration of inflammatory cytokines in wound fluids collected from patients undergoing neoadjuvant chemotherapy has been increased.79 Cytokines whose concentrations were higher include the aforementioned inflammatory factors IL-6 and TNF-α.

Further in vitro studies by Krall et al. proved that the systemic consequences of surgery can promote the outgrowth of tumour cells even at distal anatomical sites. They found out that surgery-induced tumour outgrowth was associated with a local and systemic inflammatory response characterised by the release of cytokines and the mobilization of myeloid cells into the circulation of wounded mice.80 Inflammation following the radiation therapy has also been observed in a significant fraction of patients treated for cervical cancer.81

2. Conclusions

Both carcinogenesis and inflammation are very complex processes, dependent on various types of signaling. Progress in research on inflammation revealed a connection between inflammatory processes and neoplastic transformation, the progression of tumour, and the development of metastases and recurrences (Fig. 1). In recent years several inflammation-related pathways have been described in relation to cancer, and further research into them could result in the development of therapies utilizing the knowledge on the interplay between inflammation and cancer.

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