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REVIEW ARTICLE

Inflammation and cancer: paradoxical roles in tumorigenesis and implications in immunotherapies

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Abstract Chronic inflammation caused by persistent infections and metabolic disorders is thought to contribute to the increased cancer risk and the accelerated cancer progression. Oppositely, acute inflammation induced by bacteria-based vaccines or that is occurring after cancer selectively inhibits cancer progression and metastasis. However, the interaction between inflammation and cancer may be more complex than the current explanations for the relationship between chronic and acute inflammation and cancer. In this review, we described the impact of inflammation on cancer on the basis of three perspectives, including inflammation with different durations (chronic and acute inflammation), different scopes (systemic and local inflammation) and different occurrence sequences (inflammation occurring after and before cancer). In addition, we also introduced bacteria/virus-based cancer immunotherapies. We perceive that inflammation may be a double-edged sword with cancer-promoting and cancer-suppressing functions in certain cases. We expect to further improve the understanding of the relationship between inflammation and cancer and provide a theoretical basis for further research on their complex interaction.

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Introduction

In 1828, Jean Nicolas Marjolin observed that squamous cell carcinoma developed around a post-traumatic scar tissue, suggesting that chronic inflammation was involved in cancer progression.[1] In 1863, Rudolf Virchow observed leucocytes in neoplastic tissues, which impelled researchers to associate inflammation with cancer.[2] Subsequently, Harold F Dvorak reported that cancer and inflammation shared similar signaling pathways, such as cell proliferation, survival, migration and altered angiogenesis, which were regulated by growth factors, pro-inflammatory cytokines and proangiogenic factors.[3] In recent years, epidemiological studies have shown that chronic inflammation increases the incidence of various cancers, such as liver, gastric, bladder, cervical and thyroid cancers. The use of non-steroidal anti-inflammatory drugs can reduce the risk and mortality of patients with certain cancers (such as colon and breast cancers).[4,5]

Although most evidence supports the promoting effect of inflammation in cancer, inflammation exerts anti-cancer effects in some cases. Acute inflammation is usually called 'therapeutic inflammation', wherein bacteria- and vaccines-induced immune response exerts an anti-cancer function.[6–9] Furthermore, local inflammation in patients with cancer leads to a better prognosis.[10–12] The above-mentioned studies indicate that inflammation exerts positive or negative effects on cancer based on the duration, scope and sequence of inflammation. Therefore, in this study, we described the impact of inflammation on cancer on the basis of its durations, scopes and occurrence sequences. Meanwhile, we also introduced bacteria/virus-based cancer immunotherapies.

Impact of inflammation with different durations on cancer

Inflammation is a normal pathological process that may occur in various parts of body. In the presence of a pathogen or physical or chemical stimulation, acute inflammation occurs locally to reduce damage at the site, re-establish homeostasis and support wound healing.[13] In the acute phase, blood flow and vascular permeability increase with the accumulation of inflammatory mediators and white blood cells.[14] Correspondingly, chronic inflammation often occurs without definite signs and symptoms and is often neglected until the disease becomes clinically apparent.[15] In both acute and chronic inflammation, the resident cells (such as tissue-resident macrophages; fibroblasts and stromal, endothelial, dendritic and mass cells) are activated first by various soluble factors to initiate an immune response.[16] Inflammatory agents such as cytokines, chemokines, histamines and lipid mediators trigger the migration and infiltration of inflammatory cells (e.g., natural killer [NK] cells, lymphocytes, monocytes and neutrophils), which may cause a systemic response (such as leucocytosis, fever, hypotension and cachexia).[17] Acute and chronic inflammation frequently share a similar response that involves various immune cells and soluble mediators, but their effect on cancer is distinctly different.

Chronic inflammation in cancer: always the evil

Chronic unresolved inflammation is reported to mediate the initiation and development of cancer.[18–20] Recently, approximately 25% of cancer cases have been estimated to be related to chronic inflammation.[21] Although cancer is multi-factorial in origin, various epidemiological and experimental studies suggest that some factor-induced chronic inflammatory conditions may increase the risk of cancer (Table 1):

1) Chronic inflammation caused by persistent infections from viruses, bacteria, nematodes and other microorganisms contributes to the initiation and development of cancers.[22–24] In 2018, infections constituted 13% of new cancer cases worldwide, and more than one-third of infection-related cancer cases were reported in China.[25] Infections with hepatitis B virus (HBV), hepatitis C virus (HCV), human papilloma virus (HPV) and Epstein–Barr virus (EBV) may lead to cancers such as liver and cervical cancers and nasopharyngeal carcinoma.[26–28] Approximately 80% of cases of hepatocellular carcinoma (HCC) are attributed to HBV and HCV infections.[29] More than 50% of HCC cases are reported in China, and more than 80% can be attributed to HBV infection.[30] In addition, HCC infection predominates in Africa and Asia, where HBV and HCV infections constitute approximately 60% and 20% of etiological factors of HCC, respectively.[31] Low incidence rates are reported in the United States, Europe, Egypt and Japan, where HBV and HCV infections are responsible for approximately 20% and more than 60% of HCC cases, respectively.[31] Although the mechanism remains uncertain, the HBV gene product HBV X protein (HBx) is confirmed to contribute to the viral pathogenesis and carcinogenesis of HCC by modulating the activities of several signaling pathways, such as interleukin (IL)-6/signal transducer and activator of transcription (STAT) 3, Wnt/β-catenin, mitogen-activated protein kinases (MAPK) and nuclear factor kappa-B (NF-κB) pathways.[32,33] Cervical cancer ranks fourth in terms of global female cancer incidence and mortality; it is mostly caused by HPV infection.[34] Approximately 90% of HPV infections regress spontaneously within 1–2 years, and HPV vaccination and screening can reduce HPV-related cervical cancer by more than 90%.[35] However, persistent HPV infections (mainly HPV 16 and 18) may lead to cancer.[36] Pathways such as Wnt/β-catenin, phosphatidylinositol-3-kinase (PI3K)/serine–threonine kinase (Akt), epithelial–mesenchymal transition and NF-κB[37] as well as E6 and E7 oncogenes and micro-RNAs (miRNAs) are involved in the HPV-induced cervical cancer.[38]

Similar to viruses, several bacterial infections are related to cancer as well. *Helicobacter pylori* infection is the strongest risk factor for infection-induced cancer worldwide.[25] Untreated infection with *Helicobacter pylori* leads to gastritis, peptic ulcer and eventually gastric cancer through colonization, immune escape and disease induction.[39] Although approximately 40%–80% population

Table 1 Chronic inflammation-related cancers.

Cancer	Associated inflammatory stimuli	References
Acute myeloid leukemia	Infection with VGS	46
Bladder cancer	Infection with *Schistosoma haematobium*	25
Breast cancer	Infection with GBS and obesity	63
Cervical cancer	Infections with HPV or HIV and obesity	26, 59, 68
Cholangiocarcinoma	Clonorchis sinensis and primary sclerosing cholangitis	25
Colorectal cancer	Infections with *E. coli*, *Streptococcus bovis*, *Fusobacterium nucleatum* and *Porphyromonas species*, inflammatory bowel diseases (ulcerative colitis and Crohn's disease) and obesity	41, 45, 57, 59, 67
Endometrial carcinoma	Barrett's esophagitis and obesity	59
Gall bladder carcinoma	Infection with *Salmonella*, gall bladder stone-associated chronic cholecystitis and obesity	42
Gastric cancer	Chronic gastric (*H pylori*) and obesity	25, 40
Haematologic malignancies	Infection with *Enterococci faecium*	48
Liver cancer	Infections with HBV and HCV, alcohol/non-alcohol-related liver disease and obesity	27, 31
Lung cancer	Infection with *Chlamydia pneumoniae*, COPD, inflammation caused by asbestos, infections, smoking, obesity and silica	47, 66, 72
Melanoma	UV irradiation-associated skin inflammation	80
Nasopharyngeal carcinoma	Infection with EBV	28
Oral carcinoma	Infections with *Fusobacterium nucleatum* and *Porphyromonas species*	44
Pancreatic cancer	Infections with H pylori, *Fusobacterium nucleatum* and *Porphyromonas species*, periodontal disease, pancreatitis, obesity	43
Prostate cancer	prostatitis, exposure to Cadmium and pesticides	24, 78, 79

Abbreviations: VSG, viridans group streptococci; GBS, group B streptococcal; HPV, human papilloma virus; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; *E. coli*, *Escherichia coli*; COPD, chronic obstructive pulmonary disease; UV, ultraviolet; PM2.5, particulate matter 2.5; EBV, Epstein—Barr virus; *H pylori*, *Helicobacter pylori*.

contracts the viral infection, less than 3% develop into gastric cancer.[40] Other examples include *Escherichia coli* (*E. coli*) and *Streptococcus bovis* infections that cause colorectal cancer[41]; *Salmonella* infections that cause gall bladder cancer[42]; *Fusobacterium nucleatum* and *Porphyromonas* species that cause colorectal cancer, oral carcinoma and pancreatic cancer[43—45]; viridans group streptococci (VGS) infections that cause acute myeloid leukaemia[46]; *Chlamydia pneumoniae* infections that cause lung cancer[47]; *Enterococcus faecium* infection that causes hematologic malignancies and group B streptococcus (S. GBS) infection that causes breast cancer.[48,49]

Infections activate multiple cells after being recognized by receptors such as toll-like receptors (TLRs) and nucleotide-binding oligomerization-domain protein-like receptors (NLRs).[50] These cells lead to the release of pro-inflammatory cytokines and chemokines such as IL-1β, IL-6 and IL-8, which in turn recruit and activate immune cells to produce cytokines, chemokines and free radicals.[51,52] These molecules activate host cells through signaling pathways, such as stimulator of interferon genes (STING) and NF-κB pathways, and subsequently alter the expression of anti-apoptotic, pro-proliferative and growth factors, thereby promoting cancer progression.[53,54]

2) Metabolic disorders such as obesity, type 2 diabetes mellitus, insulin resistance and non-alcoholic fatty liver disease are a hallmark of low-grade inflammation, which leads to cancer susceptibilities.[55—58] In 2015, in France, excess weight contributed to 5.4% of cancer cases, including 4500 breast cancer cases, 3400 colon cancer cases, 2500 endometrial cancer cases and 2600 kidney cancer cases.[59] In the United States of America, the incidence of obesity-related cancers increased by 7%, whereas the incidence of most other cancers decreased by 13%.[60] Metabolic diseases are characterized by abnormal cytokine production (tumor necrosis factor-α [TNF-α] and IL-6); overexpressed proteins (granulocyte macrophage colony-stimulating factor [GM-CSF] and matrix metalloproteinase [MMP] 9), infiltrated macrophages, neutrophils and eosinophils, which create a pro-tumorigenic environment resulting in accelerated cancer progression and metastasis, stimulation of angiogenesis and reduced patient survival.[61—65]
3) Inflammatory bowel disease, sepsis, prostatitis, chronic obstructive pulmonary disease (COPD) and other inflammatory diseases are considered as risk factors for cancer.[66—70] Treatment with non-steroidal anti-inflammatory agents decreases the incidence and mortality of several cancers.[4,5] Inflammatory diseases are characterized by the presence of various immune cells, epithelial cells, stromal cells, cytokines and chemokines in the micro-environment, which not only damage tissues but also promote the genetic and epigenetic alterations in normal cells to drive carcinogenesis.[71,72] Oncogenes such as Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) and several molecular signaling cascades such as NF-κB, Jak family tyrosine kinases (JAK)/

STAT, MAPK, Wnt/β-catenin and PI3K are activated in those inflammatory diseases, leading to the production of chemokines and adhesion mediators to recruit immune cells, the production of cytokines (IL-1β, IL-6, IL-17, IL-21 and TNF-α), growth factors (granulocyte colony stimulating factor [G-CSF], GM-CSF and macrophage colony stimulating factor [M-CSF]) and cyclooxygenase (COX) 2 to promote the proliferation and survival of cancer cells and the expression of proteases (MMP 7, MMP 9, MMP 10 and urokinase-type plasminogen activator [uPA]) to promote cancer invasion and metastatic escape.[73,74]

4) Environmental exposure (chemical, physical and biological stimuli) can cause a loss of homeostasis and promote a pro-neoplastic inflammatory environment.[75] Cigarette smoke induced the accumulation of airway macrophages, lymphocytes, neutrophils and monocytes, which causes chronic inflammation, thereby resulting in airway obstruction respiratory symptoms and cancer.[76] Inhalable dusts, mineral fibers and particulate matter result in oxidative stress, which initiates the synthesis of pulmonary inflammation mediators in lung epithelial cells and the activation of MAPK and NF-κB signaling pathways and eventually induces lung cancer.[77] Environmental exposure to cadmium and pesticides increases the risk of prostate cancer.[78,79] Ultraviolet (UV) radiation directly affects the skin and leads to DNA damage and reactive oxygen species (ROS) production, followed by the activation of inflammation in the skin tissue, which favors tumorigenesis.[80]

Acute inflammation in cancer: both the good and evil

In 1868, P. Bruns, a German physician, observed cancer regression in patients with severe streptococcal infection, which provided evidence for an opposite role of inflammation in the development of cancer.[81] In 1891, William Coley, an American oncologist, employed this phenomenon and successfully induced cancer regression by injecting extracts of gram-negative bacteria to patients with cancer.[82] After more than 50 years, M. Shear was the first to isolate and confirm that the active component of the bacterial extracts was lipopolysaccharide (LPS) and proved its ability to inhibit cancer progression in animals.[83] LPS stimulates the immune system by activating TLR4 and releasing TNF-α, which not only resist bacteria but also inhibit cancer progression.[84] Currently, bacteria- and virus-induced inflammatory response is designed to treat various cancers.[85,86] Bacillus Calmette-Guerin (BCG)-induced immune response was associated with cytokine secretion (IL-10/12/18, TNF-α, GM-CSF and interferon [IFN]-γ) and the accumulation of immune cells (NK cells and $CD4^+$ and $CD8^+$ T cells); BCG is widely used for urinary bladder cancer treatment.[87] *Salmonella typhimurium*, *Clostridium* and other genera were also reported to reduce cancer progression, suppress angiogenesis and metastasis and increase survival in both mouse models and human trials.[88,89]

However, evidence suggests that acute inflammation promotes cancer progression and metastasis. Standard interventional procedures of cancer diagnosis (biopsies) and treatment (surgeries) or mechanical trauma is sufficient to induce an acute local inflammatory state.[90] In such cases, inflammatory cells (macrophages, $CD4^+$ T cells and neutrophils), cytokines, chemokines and growth factors accumulate to form a distant metastatic micro-environment, which may favor cancer progression and invasion.[91] Anti-inflammatory treatments (ibuprofen) before and after biopsy significantly reduced the development of lung metastases triggered by the biopsy.[92] In addition, once acute inflammation leads to prolonged inflammation, the accompanying cancer rate may increase greatly.

Impact of inflammation with different scopes on cancer

We previously described the influence of different durations of inflammation on cancer. We now describe the relationship between inflammation with different scopes and cancer. According to the scope, inflammation can be divided into systemic inflammation and local inflammation. Inflammation can be induced by some diseases or cancer itself. Currently, it is believed that the prognosis of patients with cancer is determined not only by the characteristics of cancer itself but also by cancer-associated inflammation.[93] Systemic inflammation is closely associated with clinical symptoms, which indicate the presence and progression of cancer.[94] Cytokines, inflammatory proteins and immune cells are present and easily detectable in systemic circulation.[95] Local inflammation is confined to intra-cancer, wherein host cells, cancer cells and immune cells communicate with each other to mediate a local immune response.[96] Owing to the different scopes of inflammation, their effects are variable on the subsequent outcome of patients with cancer.

Impact of systemic inflammation on cancer

Cumulating evidence provides a proof that systemic inflammation is characterized by a cancer-promoting immune response and serves as a worse prognostic indicator for patients with cancer.[97,98] In patients with cancer, several systemic inflammation markers such as C-reactive protein (CRP) and platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are easily detectable and associated with poor survival outcomes or advanced stages in various cancers, including breast, colorectal and lung cancers (Table S1).[99–102] Diseases such as obesity cause systemic low-grade inflammation through multiple mechanisms.[103] Overnutrition leads to the rapid expansion of adipose tissues, resulting in hypoxia and endoplasmic reticulum stress.[104] Excess production of circulating insulin, leptin, steroid hormones and adiponectin activate mTOR, PI3K and MAPK pathways, thus promoting cancer progression.[105] In addition, altered intestinal microbiota activates TLR signaling pathway and immune cells, thereby releasing various cytokines into systemic circulation.[106] The resulting sustained inflammatory response may promote the initiation and development of cancer. In patients with cancer, obesity also contributes to an increased risk of recurrence and poor survival outcomes.[107,108]

Table 2 Bacteria-based therapies in cancer treatment.

Bacteria-based therapy	Cancer	Status
BCG	Bladder cancer	FDA approved
MPLA	HPV-induced CC	FDA approved
APS001F	Advanced or metastatic solid tumors	Phase I and II clinical trial (NCT01562626, recruiting)
C. novyi NT	Solid tumors	Phase I clinical trial (NCT01924689, completed)
C. novyi NT	Solid tumors	Phase I clinical trial (NCT01118819, terminated)
C. novyi NT	Tumors	Phase I clinical trial (NCT00358397, terminated)
Klebsiella pneumoniae (QBKPN SSI)	NSCLC	Phase II clinical trial (NCT02256852, completed)
L. monocytogenes (ADXS11-001)	CIN	Phase II clinical trial (NCT01116245, terminated)
L. monocytogenes (ADXS11-001)	CC, recurrent CC	Phase II clinical trial (NCT01266460, active, not recruiting)
L. monocytogenes (ADXS11-001)	HPV-16 +ve oropharyngeal carcinoma	Phase I clinical trial (NCT01598792, terminated)
L. monocytogenes (ADXS11-001)	Head and neck cancer, HNSCC, HPV positive oropharyngeal SCC	Phase II clinical trial (NCT02002182, active, not recruiting)
L. monocytogenes (ADXS11-001)	Metastatic/recurrent and stage IVA, IVB and III CC, cervical adenosquamous cell carcinoma, cervical SCC, cervical small cell carcinoma	Phase I and II clinical trial (NCT02164461, completed)
L. monocytogenes (ADXS11-001)	Anal and rectal cancer	Phase II clinical trial (NCT02399813, completed)
L. monocytogenes (ADXS11-001)	High risk and advanced CC	Phase II clinical trial (NCT02853604, active, not recruiting)
L. monocytogenes (ADU-623)	Astrocytic tumors, GBM, AA, brain tumor	Phase I clinical trial (NCT01967758, completed)
L. monocytogenes (CRS-100)	Metastatic cancer and liver cancer	Phase I clinical trial (NCT00327652, completed)
L. monocytogenes (CRS-207)	Malignant epithelial mesothelioma, adenocarcinoma of the pancreas and ovaries, NSCLC	Phase I clinical trial (NCT00585845, terminated)
L. monocytogenes JNJ-64041757	NSCLC	Phase I clinical trial (NCT02592967, terminated)
L. monocytogenes JNJ-64041809	Castration-resistant prostate neoplasms	Phase I clinical trial (NCT02625857, completed)
L. monocytogenes pLADD	CRC	Phase I clinical trial (NCT03189030, active, not recruiting)
S. Typhimurium (VNP20009)	Unspecified adult solid tumor	Phase I clinical trial (NCT0004216, completed)
S. Typhimurium (VNP20009)	Cancer and metastatic cancer	Phase I clinical trial (NCT0004988, completed)
S. Typhimurium (VNP20009)	Unspecified adult solid tumor	Phase I clinical trial (NCT0006254, completed)
S. Typhimurium (VNP20009)	Liver cancer, biliary cancer	Phase I clinical trial (NCT01099631, completed)
S. Typhimurium (VXM01)	Stage IV pancreatic cancer	Phase I clinical trial (NCT01486329, completed)
S. Typhimurium (VXM01)	CRC	Phase I clinical trial (NCT02718430, completed)
S. Typhimurium (VXM01)	Glioblastoma	Phase I clinical trial (NCT02718443, completed)
Streptococcus pyogenes and *Serratia marcescens*	Melanoma, sarcoma, GIST, head and neck cancer, TCC, prostate cancer, ovarian	Phase I clinical trial (NCT00623831, completed)

(*continued on next page*)

Table 2 (*continued*)

Bacteria-based therapy	Cancer	Status
	carcinoma, esophageal cancer, breast cancer	
DTP, BCG, Measles virus, *Serratia marcescens* and *Streptococcus pneumoniae*	Lung cancer	Phase I and II clinical trial (NCT02333474, completed)

Abbreviations: BCG, Bacillus Calmette-Guerin; MPLA, Monophosphoryl lipid A; HPV, human papillomavirus; CC, cervical cancer; C., Clostridium; L., Listeria; CNS, central nervous system; NSCLC, non-small cell lung cancer; CIN, cervical intraepithelial neoplasia; HNSCC, head and neck squamous cell carcinoma; SCC, squamous cell carcinoma; 5-FU, fluorouracil; MPM, malignant pleural mesothelioma; GAC, gastric adenocarcinoma; EAC, esophageal adenocarcinoma; CRC, colorectal cancer; GBM, glioblastoma multiforme; AA, anaplastic astrocytoma; S., Salmonella; GIST, gastrointestinal stromal tumor; TCC, transitional cell carcinoma; DTP, Diphtheria.

The mechanism of cancer-induced systemic inflammation remains unclear; it may attribute to a non-specific response induced by cancer hypoxia/necrosis or oncogene mutations. For instance, mutations of KRAS or tumor protein (TP) 53, may directly induce the transcription of key pro-inflammatory pathways.[109,110] Cancer cells and immune cells infiltrated in cancer tissues release various mediators (IL-6, IL-8, vascular endothelial growth factor [VEGF], M-CSF and GM-CSF), which contributed to systemic inflammation by activating the JAK/STAT pathway and result in the expansion of immature myeloid cells and inactivation or tolerance of cytotoxic T cells.[111] Neutrophils, myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) accumulate in the circulation and peripheral tissues, inhibit lymphocyte function and form an immunosuppressive macrophage phenotype, thereby forming a positive feedback loop and amplifying the entire process.[112] Sustained systemic inflammation further leads to the recruitment and accumulation of immune cells and soluble factors that maintain proliferation, metastasis and neovascularization while suppressing anti-cancer function.[113] This is the mechanism by which inflammation and cancer initiate and sustain each other. Excess inflammatory mediators result in alterations in body metabolism and neurological and endocrine functions, leading to cancer cachexia syndromes that causes weight loss, fatigue, anorexia and fevers.[114]

Impact of local inflammation on cancer

Several studies emphasized that local inflammation, measured based on the density of tumor-infiltrating lymphocytes (TILs), indicated a better prognosis in multiple cancers.[115,116] TILs, consisting of a heterogeneous population of lymphocytes such as T cells, B cells, macrophages and NK cells, are localized in the cancer stroma or intraepithelium.[117] The densities of $CD3^+$ and $CD8^+$ TILs exhibited a positive relationship with improved cancer survival, while the effect of TIL-B cells and CD4 TILs was not consistent. Given the positive role of TILs in cancer prognosis, researchers considered mobilizing TILs for cancer treatment. TILs from patients' blood, lymph nodes or cancer tissues were expanded *ex vivo* and were adoptively transferred into cancer patients through preparative lymphodepletion and subsequent support of IL-2.[118] With this treatment, an approximately 50% response rate was achieved in patients with metastatic melanoma.[119] In order to achieve individualized cancer treatments, T cells from peripheral blood were genetically modified for developing T cell receptor-engineered T cell (TCR-T) and chimeric antigen receptor T cell (CAR-T) therapies. Adoptive transfer of modified $CD4^+$ T cells into cancer-bearing mice recruited and activated dendritic cells and subsequently primed $CD8^+$ TILs to exert continuous cytotoxicity to cancers.[120]

Local treatment-induced inflammation was recently used in combination therapies for cancer. A sub-population of cancer is called 'cold' cancer, which exhibits a non-inflamed micro-environment and low response rates to immunotherapy.[121] Bacteria/virus-based vaccines (BCG and T-vec) selectively accumulate and replicate in cancer and induce an inflammatory response confined to cancer tissues.[122] Combined with chemotherapy, radiotherapy and immunotherapy (cytotoxic T-lymphocyte antigen [CTLA]-4 or programmed cell death protein-1 [PD-1] blockade), these vaccines may induce an inflammatory microenvironment that consists of increased active anticancer T cells and various molecules (IL-2, TNF and IFN), significantly suppress the progression of poorly immunogenic cancer and prolong the overall survival of patients.[123,124]

However, in some cases, local inflammation may serve as a 'fertile soil' to allow cancer progression and metastasis.[125] For instance, physical trauma, which evoked local inflammation and wound healing reaction, induced an inflammatory milieu of cytokines, chemokines and growth factors that augmented angiogenesis and favored cancer invasion and evasion of immune surveillance.[126,127] Carrageenan-induced acute local inflammation promoted cancer progression by increasing the expression of prostanoids and pro-inflammatory cytokines.[128]

Impact of inflammation with different sequences on cancer

In addition to the duration and scope of inflammation, the sequence of inflammation is also crucial in cancer development. Chronic inflammation, whether occurring before or after cancer, can promote the occurrence, development and metastasis of cancer. However, the role of inflammation with other forms remains uncertain. The inflammation-then-cancer and reverse cancer-then-inflammation models may lead to opposite effects on cancer progression, and also induced different intra-tumoral immune infiltration.

Table 3 Virus-based therapies in cancer treatment.

Virus-based therapy	Cancer	Status
IMQ	Basal cell carcinoma	FDA approved
T-vec	Melanoma	FDA approved
Adenovirus		
CG0070	TCC, bladder cancer	Phase I clinical trial (NCT00109655, unknown)
CG0070	TCC, bladder cancer, carcinoma in situ with or without papillary tumors	Phase II and III clinical trial (NCT01438112, terminated)
CG0070	Bladder cancer	Phase II clinical trial (NCT02365818, completed)
DNX-2401	Brain cancer	Phase I clinical trial (NCT00805376, completed)
DNX-2401	Glioblastoma or gliosarcoma	Phase I clinical trial (NCT02197169, completed)
DNX-2401	Brain glioma	Phase I clinical trial (NCT03178032, completed)
DNX-2401	Recurrent high-grade glioma	Phase I clinical trial (NCT03896568, recruiting)
Enadenotucirev	Solid tumors of epithelial origin, metastatic CRC, metastatic bladder cancer	Phase I and II clinical trial (NCT02028442, completed)
LOAd703	Pancreatic cancer	Phase I and II clinical trial (NCT02705196, recruiting)
LOAd703	Pancreatic cancer, ovarian cancer, biliary carcinoma, CRC	Phase I and II clinical trial (NCT03225989, recruiting)
OBP-301	Hepatocellular carcinoma	Phase I clinical trial (NCT02293850, recruiting)
OBP-301	Stage III and IV melanoma	Phase II clinical trial (NCT03190824, active, not recruiting)
ONCOS-102	Solid tumors	Phase I clinical trial (NCT01598129, completed)
VCN-01	refractory retinoblastoma	Not applicable (NCT03284268, recruiting)
Coxsackievirus		
CAVATAK	Solid tumors	Phase I clinical trial (NCT00636558, completed)
CAVATAK	Head and neck cancer	Phase I clinical trial (NCT00832559, terminated)
CAVATAK	Stage IIIc and IV melanoma	Phase II clinical trial (NCT01227551, completed)
CAVATAK	Melanoma	Phase I clinical trial (NCT01636882, completed)
CAVATAK	Non-small invasive bladder cancer	Phase I clinical trial (NCT02316171, completed)
CAVATAK	Advanced/metastatic melanoma	Phase II clinical trial (NCT04152863, recruiting)
HSV		
G207	Recurrent brain cancer	Phase I and II clinical trial (NCT00028158, completed)
G207	Progressive or recurrent supratentorial brain tumor	Phase I clinical trial (NCT02457845, recruiting)
G207	Recurrent or refractory cerebellar brain tumors	Phase I clinical trial (NCT03911388, recruiting)
NV1020	CRC metastatic to the liver	Phase I and II clinical trial (NCT00149396, completed)
M032	Recurrent malignant glioma	Phase I clinical trial (NCT02062827, recruiting)
HSV1716	Non-CNS solid tumors	Phase I clinical trial (NCT00931931, completed)
HSV1716	Malignant pleural mesothelioma	Phase I and II clinical trial (NCT01721018, completed)
HF10	Refractory head and neck cancer or solid tumors with cutaneous and/or superficial lesions	Phase I clinical trial (NCT01017185, completed)
HF10	Solid tumors	Phase I clinical trial (NCT02428036, completed)
rQNestin	Recurrent malignant glioma	Phase I clinical trial (NCT03152318, recruiting)
C134	recurrent GBM	Phase I clinical trial (NCT03657576, recruiting)
RP1	Melanoma (skin, uveal, ocular), bladder cancer, non-melanoma skin cancer	Phase I and II clinical trial (NCT03767348, recruiting)
RP1	Advanced cutaneous SCC	Phase I clinical trial (NCT04349436, not yet recruiting)
GEN2	Hepatocellular carcinoma, metastatic cancer	Phase I clinical trial (NCT04313868, recruiting)
ONCR-177	Advanced or refractory cutaneous, subcutaneous or metastatic nodal solid tumors	Phase I clinical trial (NCT04348916, recruiting)

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Table 3 (*continued*)

Virus-based therapy	Cancer	Status
T3011	Advanced cutaneous or subcutaneous malignancies	Phase I clinical trial (NCT04370587, not yet recruiting)
MV		
MV	Advanced NSCLC	Phase I and II clinical trial (NCT008282022, unknown)
MV-CEA	Recurrent GBM	Phase I clinical trial (NCT00390299, completed)
MV-NIS	Ovarian and primary peritoneal cavity cancer	Phase I clinical trial (NCT00408590, completed)
MV-NIS	Malignant pleural mesothelioma	Phase I clinical trial (NCT01503177, active, not recruiting)
MV-NIS	Recurrent or metastatic SCC of the head and neck cancer, metastatic breast cancer	Phase I clinical trial (NCT01846091, active, not recruiting)
MV-NIS	Multiple myeloma	Phase II clinical trial (NCT02192775, completed)
MV-NIS	Ovarian, fallopian, or peritoneal cancer	Phase II clinical trial (NCT02364713, recruiting)
MV-NIS	Recurrent malignant peripheral nerve sheath tumor	Phase I clinical trial (NCT02700230, recruiting)
MV-NIS	Recurrent Medulloblastoma or ATRT	Phase I clinical trial (NCT02962167, recruiting)
MV-NIS	Bladder cancer	Phase I clinical trial (NCT03171493, recruiting)
MV mixed vaccine	Lung cancer	Phase I and II clinical trial (NCT02333474, completed)

Abbreviations: IMQ, Imiquimod; T-vec, Talimogene laherparepvec; TCC, transitional cell carcinoma; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma; HSV, herpes simplex virus; CAVATAK, coxsackievirus 21; CNS, central nervous system; GBM, glioblastoma multiforme; MV, measles virus; MV-CEA, carcinoembryonic antigen-expressing measles virus; MV-NIS, measles virus genetically engineered to produce human thyroidal sodium iodine symporter; MSC, mesenchymal stem cells; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; ATRT, atypical teratoid/rhabdoid tumor.

Sepsis, resulting from acute severe infections, exerts a dysregulated inflammatory reaction in the early stage and an immunosuppressive response in the late stage, which is very similar to immune dysregulation of cancer.[129] Recently, some researchers reported that patients who survived bacterial sepsis were more likely to develop malignancies.[130–132] Researchers established a sequential double-hit mice model of polymicrobial sepsis followed by subcutaneous cancer inoculation and found that sepsis promoted cancer development with an increase in cancer-associated granulocytic MDSCs, Tregs or macrophages.[133–135]

However, when the sequence was reversed by establishing a cancer-then-sepsis mice model, researchers observed that local and metastatic cancer progression was inhibited by TLR 4-related-enhanced NK cell viability.[136] Chen et al. infected cancer-bearing mice with a malaria parasite and found that cancer progression and metastasis were significantly inhibited.[137] Furthermore, a clinical study demonstrated that when nine patients with bladder cancer received intra-vesical administration of coxsackievirus 21 (CAVATAK), one patient achieved complete resolution of cancer.[138] CAVATAK caused evident inflammatory changes within non-muscle invasive bladder cancer tissues through the upregulation of immune checkpoint-inhibitory genes such as programmed cell death ligand-1 (PD-L1) and lymphocyte-activation gene 3 (LAG3) and induction of the innate activator retinoic acid inducible gene-1 (RIG-1).[138] However, when BALB/C mice bearing 4T1 lung metastases were intra-peritoneally injected with 10 mg of LPS, lung weight and pleural lesions of mice were increased, which was accompanied by increased angiogenesis and vascular permeability.[139,140] The experimental results suggest that inflammation exerts either a potent pro-cancer function or inhibits cancer progression and metastatic spread, depending on the cancer line and stage and experimental model.

Bacteria/virus-based cancer immunotherapies

BCG, imiquimod and T-vec were approved by the Food and Drug Administration (FDA) for the treatment of bladder cancer, basal cell carcinoma and melanoma, respectively.[141,142] Monophosphoryl lipid A (MPLA) was approved by the FDA for use in vaccines for preventing cancers such as cervical cancer.[143] Other bacteria and viruses used alone or in combination have entered the clinical trials for cancer treatment (Table 2 and Table 3). As mentioned before, bacterial or viral therapies possess reliable prospects for treating cancer. Bacteria such as *Salmonella*, *Listeria monocytogenes* and *Clostridium* and viruses such as myxoma virus and reovirus, prefer to grow in the hypoxic environment of solid tumors.[144,145] Yu et al. found that gram-negative or gram-positive bacteria injected intravenously into mice with syngeneic and xenogeneic cancer as well as spontaneous cancer entered and replicated in the cancer tissue.[146] In addition, the clearance of bacteria and virus is inhibited in cancer owing to impaired immunosurveillance or abnormal signaling pathways (IFN, TLR and JAK/STAT).[147] Furthermore, besides the direct anti-cancer function, the immune response induced by bacteria and viruses is conducive to cancer elimination.[148,149] Oncolytic viruses and *C.*

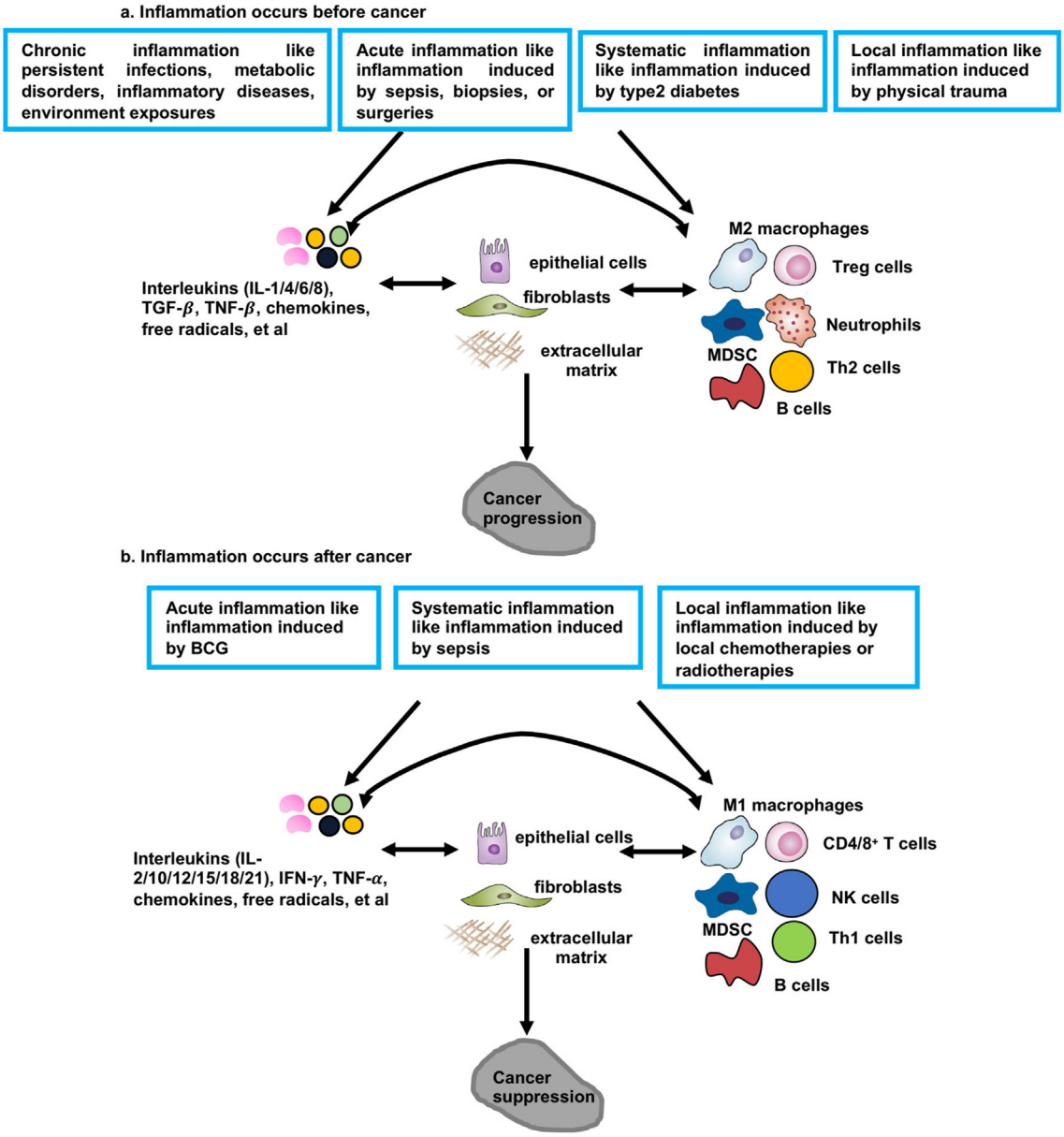

Figure 1 The impact of inflammation on cancer. Inflammation may exert either a potent pro-cancer function or may inhibit cancer progression and metastatic spread, depending on the duration, scope and sequence of inflammation. **(A)** Several inflammatory conditions promoted cancer progression if inflammation occurred before cancer; **(B)** Several inflammatory conditions inhibited cancer progression if inflammation occurred after cancer.

novyi or *Salmonella* infections lead to the release of novel tumor antigens and the expression of pathogen-associated and damage-associated molecular patterns, which promote the maturation of dendritic cells and subsequent activation of NK and $CD8^+$ T cell-mediated anti-tumor response.[150,151] Moreover, *Salmonella* infection downregulates the number of Tregs and inhibits angiogenesis to alter the immunosuppressive micro-environment and delay cancer progression.[152] In addition, some bacteria and viruses can be used as vectors to carry drugs for enhancing cancer immunotherapy.[9] *E. coli*, engineered to release the nanobody antagonist of CD47 in the tumor site, activates the tumor-infiltrating T cells and results in reliable and systemic anti-tumor immunity and rapid tumor regression.[153]

Conclusions and future perspectives

The effects of inflammation on cancer are significantly different; therefore, different situations should be considered to suppress or promote inflammation for achieving the best response (Fig. 1). Regardless of the form of inflammation, as long as it occurs before the cancer, it should be suppressed. Chronic inflammation is always detrimental. Anti-inflammatory measures like non-steroidal drugs and specialized pro-resolving lipid mediators should be used to prevent the risk and incidence of inflammation-related cancer and avoid the progression from acute inflammation to persistent-chronic inflammation.[154] However, when inflammation occurs after cancer

formation, factors such as the cause of inflammation and the duration of inflammation should be considered to inhibit or employ inflammation. Surgery- or biopsy-induced wound can stimulate cancer growth via inflammation and angiogenesis, while an acute inflammatory response initiated by recombinant cytokines, TLRs activators and chemotherapeutic agents can effectively promote the infiltration of inflammatory cells into tumor tissues and activate dendritic cell (DC)-mediated anti-tumor T-cell response, slowing the growth of cancer and enhancing the efficacy of anti-cancer therapies.[155–157]

Furthermore, although different types of inflammation that cause different outcomes of cancer seem to share similar responses, the involved molecules and immune cells will exert different effects. The increased expression of TNF-α in chronic inflammation induces intact TNF/TNF receptor (TNFR) complex and activates the NF-κB signaling pathway, which further promote cell survival and tumor growth.[158] However, local administration of TNF-α-caused-acute inflammation induces apoptosis of cancer cells and tumor regression, which is related to the form of modified complex.[159,160] Cancer-promoting inflammation selectively recruit various immune cells such as MDSCs, Tregs, tumor-associated fibroblasts and macrophages, which inhibit the CTLs-mediated response, dampen immune surveillance and facilitate the formation of immunosuppressive tumor microenvironments.[161] While cancer-inhibiting inflammation induces the M1 polarization of macrophages, promotes the antigen presentation ability of DCs and the infiltration of NK cells, which subsequently active adaptive immunity and eliminate cancer.[162,163] Therefore, the essence of inflammation-targeting cancer therapy is how to accurately identify the type of inflammation and selectively promote cancer-inhibiting inflammation and inhibit cancer-promoting inflammation. More studies are also needed to elucidate the interplay between inflammation and cancer.

Author contributions

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Conflict of interests

The authors declare no conflict of interests.

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Appendix A. Supplementary data

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