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REVIEW

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Role of signaling pathways in the interaction between microbial, inflammation and cancer

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Abstract

Microbial-induced inflammation serves a dual role, safeguarding against pathogens but also posing a risk of secondary harm to host tissues, potentially leading to fibrosis and cancer. Beyond traditional pathogens, gut microbiota, the mutualistic microorganisms inhabiting the gastrointestinal tract, crucial for digestion, immunity, and cancer prevention, can incite inflammation-related cancer when their microenvironment undergoes changes. Recent research reveals that microbiota members like *Escherichia coli* and other genotoxic pathogens can induce DNA damage across various cell types. Chronic infections involving microbiota members like *Helicobacter* spp., linked to liver, colorectal, cervical cancers, and lymphoma, can activate carcinogenic processes. Inflammatory responses, driven by immune cells releasing inflammatory molecules like macrophage migration inhibitory factor (MMIF), superoxide peroxynitrite, pro-inflammatory cytokines, adhesion molecules, and growth factors, contribute to DNA damage and oncogenic mutations accumulation. This microenvironment further supports neoplastic cell survival and proliferation. This summary discusses the involvement of inflammatory pathways in microbial-triggered carcinogenesis and the potential role of microbiota modulation in cancer prevention.

Keywords Signaling pathways, Microbe, Infection, Inflammation, Carcinogenesis, Cancer

1 Introduction

In response to pathogens or irritants, the body initiates "inflammation" to protect tissues and fight infections. Tissue-resident mononuclear phagocytes are the first responders in the innate immune response, identifying pathogens and tissue damage using pattern recognition receptors (PRRs). These receptors detect pathogen-associated molecular patterns (PAMPs) such as microbial nucleic acids, bacterial cell wall lipopolysaccharide (LPS), proteoglycans, fungal cell wall components like α-mannan and β-glucan, and danger-associated molecular patterns (DAMPs) released by injured cells, including nucleic acids, uric acid, ATP, amyloid β, and S100 family cytoplasmic proteins [1, 2].

PRR signaling is crucial, releasing factors that activate and recruit immune cells like monocytes, neutrophils, and lymphocytes to infection or damage sites during persistent challenges [2–5]. Initial vascular changes involve secreted factors like prostaglandins and nitric oxide, causing vasodilation to increase blood flow and facilitate leukocyte transport. Inflammatory mediators like histamine and leukotrienes boost vascular permeability, allowing plasma proteins and leukocytes to exit circulation. Pro-inflammatory cytokines like interleukin

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1 (IL-1) and tumor necrosis factor alpha (TNF-α) drive immune cell infiltration, guided by chemoattractant factors. Activated immune cells combat invaders while promoting swelling and phagocytic activity to protect injured areas [6, 7].

Inflammation subsides after pathogen removal but can persist in chronic infections or with continuous DAMP exposure [4, 8, 9], causing tissue fibrosis and cancer. The link between inflammation and cancer dates back to 1863, with Virchow noting cancer development at chronic inflammation sites [10]. Epidemiological data strongly connect chronic inflammation to higher cancer risk [11, 12]. Roughly two million cancer cases yearly result from infectious agents [13], including human papillomaviruses, hepatitis B and C viruses, and *Helicobacter pylori* in the gut microbiota, responsible for a third of infection-related cancers like gastric, liver, colorectal, and cervical cancers [14, 15]. Non-mutualistic microorganisms and gut microbiota can also trigger inflammatory responses in various cancer types, including leukemia [16–18] and lymphoma [19–21].

This review summarizes recent findings on pathways linking pathogen-triggered inflammation to cancer onset and progression while exploring modulating gut microbiota for cancer prevention.

2 Pathogens and cancer: protective effects of inflammation and mutagenic potential

2.1 Microbiota and susceptibility to infection

While the body encounters microorganisms regularly, only a fraction are pathogenic or evade the immune response, with many establishing mutually beneficial relationships. An example is the gut microbiota, residing in the gastrointestinal tract [5].

Commensal microorganisms on body surfaces and in the gut play crucial roles in various functions, including immune response, energy metabolism, and cancer prevention [14, 22]. Disruption of their microenvironment can lead to breaches in the skin or intestinal mucosa, entering the bloodstream, and causing chronic inflammation, tissue fibrosis, and eventually cancer [23]. Certain commensal bacteria, like *Fusobacterium varium*, *Bacteroides vulgatus*, *Escherichia coli*, and *Clostridium clostridioforme*, invade colonic epithelial cells, triggering host inflammatory reactions. They adhere to and invade colonic epithelial cells, leading to the expression of mRNAs for inflammatory cytokines like IL-8, IL-6, TNF-α, and CCL2, as well as the release of IL-8 and TNF-α by host cells [24]. Studies have also observed increased expression of these cytokines in inflamed epithelia in ulcerative colitis patients.

Additionally, *Helicobacter pylori*, protective against pathogenic bacteria and esophageal cancer [14], can contribute to stomach cancer in cases of chronic inflammation [25]. Recent mouse studies indicate that *H. hepaticus* promotes tumorigenesis [15]. Similarly, *E. coli*, which induces mucosal immune responses, can cause inappropriate immune activation in genetically susceptible hosts, leading to colitis-associated colorectal cancer [22]. *E. coli* from mice with intestinal inflammation alters gene expression in commensal gut bacteria [26]. Investigating these mechanisms may unveil therapeutic targets for patients with inflammatory bowel diseases and colitis-associated colorectal cancer.

Various microbiota bacteria implicated in inflammation-mediated carcinogenesis are listed in Table 1. Changes in gut microbiota composition, driven by *E. coli* (Fig. 1A), may increase susceptibility to invasion by non-microbiota pathogens like *Neisseria* spp., Hepatitis C virus, *Candida albicans*, and *Giardia intestinalis*, promoting malignant transformation in various cell types, including melanoma and carcinoma epithelial cells, lymphocytes in lymphoma, and other blood cancers [20, 21, 27–35] (Fig. 1B, C).

The question of why and how microbiota members become pathogenic and contribute to chronic inflammatory diseases leading to cancer has puzzled the scientific community for decades. Hypotheses suggest the microbe-poor urban environment may impact immune function and inflammation-mediated carcinogenesis [54]. Inflammatory cytokines, particularly IL-23 released by T-helper 17 (Th17) cells, are linked to tumor-associated inflammation. However, the precise mechanisms connecting the Th17/IL-23 axis and carcinogenesis remain

Table 1 Various microbiota bacteria causing inflammation-associated carcinogenesis

Bacteria	Types of cancer
Bacillus spp	Bladder cancer [36]
Bacteroides spp.	Colorectal cancer [37–39]
Enterobacter spp.	Solid [40–42] and blood cancers [33, 34]
Enterococcus spp.	Solid cancers [41, 43, 44]
Escherichia coli	Breast [45], bladder [36], and colorectal [22, 46] cancers, renal cell carcinoma [32], acute myeloid leukemia [16]
Helicobacter spp	Gastric, liver, cervical [13, 25], esophageal [14], and colon [15] cancers, lymphoma [19, 47]
Klebsiella spp	Solid cancers [41, 48]
Pseudomonas spp.	Solid [41, 46, 48, 49] and blood cancers [50–53]

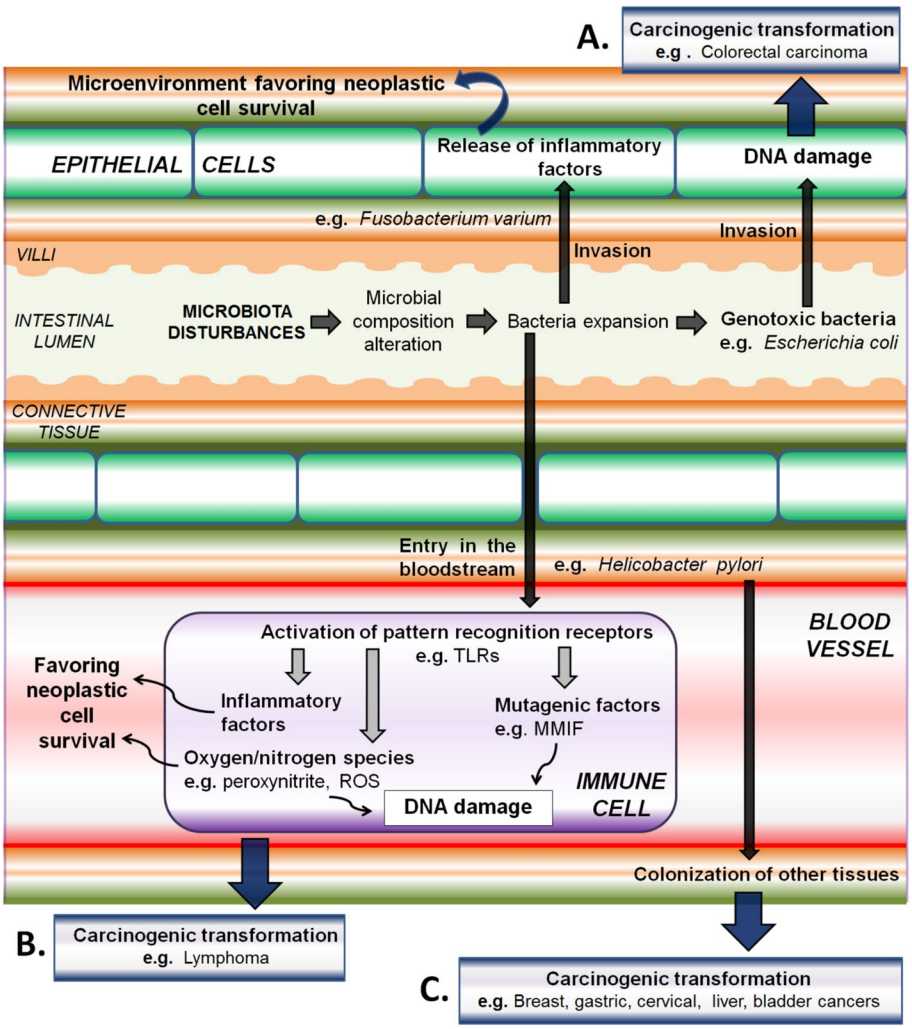

Fig. 1 Gut microbiota and carcinogenesis. Gut microbiota, a group of microorganisms permanently inhabiting the gastrointestinal tract and which plays a key role in digestion, immunity, and cancer prevention [14, 22] can promote malignant transformation of various cell types following alterations of their microenvironment. In colorectal carcinoma genesis (**A**), epithelial cells invaded by genotoxic bacteria start their transformation following DNA damage and produce inflammatory factors favoring neoplastic cell survival. In lymphomagenesis (**B**), the transformation of invaded lymphocytes starts following DNA damage induced by genotoxic bacteria that have entered the bloodstream. Affected immune cells produce a large amount of pro-inflammatory factors that favor neoplastic cell survival. Similarly, genotoxic bacteria can infect several other cell types that they reach transported by the bloodstream, resulting eventually in breast, gastric, cervical, liver, and bladder cancers (**C**), for instance. MMIF: macrophage migration inhibitory factor. ROS: reactive oxygen species. TLRs: Toll-like receptors

unclear. Th17 cells are associated with inflammation and abnormal angiogenesis in various cancer types, including leukemia [55]. Regulatory T cells may inhibit the function of Th17 cells, strengthening the inflammatory cell regulatory network and preventing chronic inflammation in the presence of environmental microbiota [56, 57]. Reduced exposure to environmental microbiota might facilitate chronic inflammation. Signaling pathways contributing to inflammation-mediated carcinogenesis triggered by microbiota bacteria and other pathogens are explored in subsequent sections.

2.2 Outcome of immune defense against pathogens: mutagenic responses and cancer

Numerous pathogens, including *Trypanosoma brucei*, fungi like *Cryptococcus neoformans* and *Aspergillus fumigatus*, bacteria, and viruses, can induce chronic inflammation [58–60]. As discussed earlier, emerging evidence strongly links cancer with microbiota (Table 1) and other pathogens that establish chronic inflammation (Table 2). This summary focuses on fundamental findings bridging pathogen-triggered inflammatory pathways and cancer development.

Table 2 Various non-microbiota pathogens causing inflammation-associated carcinogenesis or aggravating cancer aggressiveness

		Types of cancer
Viruses	Cytomegalovirus	Glioblastoma [61], prostate cancer [62]
	EBV	AIDS-related lymphoma [35], immunoblastic lymphoma [63], Kaposi's sarcoma [64]
	HBV, HCV	Gastric, liver, cervical cancers [13, 65]
	Herpesviruses	Kaposi's sarcoma [64, 66], melanoma [31]
	HIV	Kaposi's sarcoma [64], plasmablastic lymphoma [20, 21, 35]
	Leukemia viruses	T-cell leukemia [67], prostate cancer [62]
	HPV	Gastric, liver, cervical [13, 42, 68], prostate [62] cancers
Bacteria	*Acinetobacter* spp	Solid [36, 49, 69] and blood cancers [70]
	Aeromonas spp.	solid [71] and blood cancers [72, 73]
	Neisseria spp.	prostate [74] and cervical [30] cancers
	Propionibacterium spp.	Gastric [42], prostate [62, 74, 75] cancers
	Staphylococcus aureus	solid cancers [36, 46, 48, 49]
Fungi	*Candida* spp.	leukemia [17, 18], other blood cancers [76]
	Opportunistic yeast	Solid and blood cancers [77]

EBV Epstein-Barr virus, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *HIV* Human immunodeficiency virus, *HPV* Human papillomavirus

The mechanisms by which microbial pathogens contribute to cancer are intricate, involving interactions between chronic inflammation, direct microbial effects on host cells, and changes in tissue homeostasis. Inflammatory responses that successfully eliminate PAMPs and DAMPs are actively terminated, initiating the healing process. Phagocytosis of apoptotic cells enhances anti-inflammatory mediator production, promoting an anti-inflammatory response [78]. Conversely, impaired phagocytosis can promote inflammation, recruiting more immune cells [79], highlighting crosstalk between inflamed tissue and immune cells mediated by anti- and pro-inflammatory factors produced by both resident and infiltrating cells [80, 81]. Studies in a rat model revealed a shift from antibacterial tissue damage to tissue repair involving factors with dual pro-inflammatory and anti-inflammatory effects, dependent on the microenvironment [82, 83]. Such factors have been observed in humans, including metalloproteinases, transforming growth factor-α, prostaglandin E2, and reactive oxygen/nitrogen species [84–88].

Failure to terminate the inflammatory response leads to chronicity, characterized by inflammatory foci dominated by lymphocytes, plasma cells, and macrophages, producing abundant cytokines, chemokines, growth factors, and reactive oxygen/nitrogen species, causing continuous tissue damage [89]. Reactive oxygen/nitrogen species released in these conditions can produce mutagenic agents like peroxynitrite (ONOO-), which damages DNA and predisposes to neoplasia [90–92]. Pro-inflammatory cytokines like TNF-α and macrophage migration inhibitory factor (MMIF) released by macrophages and T-lymphocytes exacerbate DNA damage and interfere with protective responses [93–95]. The inflammatory microenvironment supports neoplastic cell survival and proliferation [80, 81], suggesting that modulating factors fueling chronic inflammation may have anti-cancer effects.

Interestingly, some commonly used antineoplastic agents causing DNA damage-induced apoptosis in sensitive cells also exhibit antibacterial activities against pathogens like *Acinetobacter* spp. [70], associated with various solid and blood cancers [36, 49, 69]. Agents like vincristine, cisplatin, and doxorubicin indicate the complexity of interactions between cancer-related pathogens and transforming cells. Eradication of the Gram-negative bacterium *Campylobacter jejuni* in immunoproliferative small bowel disease suppresses inflammation-mediated lymphomagenesis [19]. Future studies exploring the relationship between bacteria and transforming cells may shed light on bacteria-triggered inflammation and subsequent carcinogenic processes.

3 Pattern-recognition receptors: example of Toll-like receptors

3.1 TLR signaling and inflammation

TLRs detect bacterial, viral, and parasite PAMPs either extracellularly (TLR1, 2, 4–6, 11) or within endolysosomes (TLR3, 7–9, 10). They recognize various PAMPs/DAMPs, even including "self" molecules like heat shock proteins and fibrinogen, linking TLR-triggered inflammation to autoimmune diseases [96, 97]. Upon stimulation, TLRs initiate signaling cascades activating transcription factors: AP-1, NF-κB, and interferon regulatory factors (IRFs). TLR signaling happens in the cytoplasm through Toll/IL-1 receptor (TIR) domains, serving as docking

sites for TIR-containing cytoplasmic adaptors, crucial for signal transduction. These adaptors include MyD88, MyD88 adaptor-like (MAL), TIR-domain-containing adapter-inducing interferon-β (TRIF), TRIF-related adaptor molecule (TRAM), and the TLR pathways' negative regulator, SARM (sterile-alpha and Armadillo motif containing protein) [98, 99]. MyD88 engages all TLRs except TLR3, either directly (TLR5, 7–11, TLR1-TLR2, TLR2-TLR6) or with MAL/TIRAP (e.g., TLR4, TLR1-TLR2, TLR2-TLR6).

MyD88 signaling employs a death domain (DD) that interacts with IRAK4's DD, inducing autophosphorylation and binding to IRAK1 and 2 [100]. This complex includes E3 ubiquitin ligases TRAF6, cIAP1, cIAP2, and E2 ubiquitin-conjugating enzyme Ubc13 in TLR4 [101, 102]. TRAF6 catalyzes polyubiquitin chain formation, leading to K63-linked polyubiquitination of cIAPs and recruitment of adaptor proteins TAB2 and 3, activating MAPK kinase-kinase TAK1 (transforming growth factor-β-activated kinase 1) [102, 103]. K63-linked polyubiquitin also binds NF-κB inhibitor kinase complex (NEMO/IKK-γ), recruiting it to the TLR4 signaling complex [104]. Activated TAK1 activates downstream MAPKs p38α and JNK, associated with inflammation-mediated carcinogenesis and pro-inflammatory mediator expression [66, 105–108].

IKK activates NF-κB transcription factor, triggering transcriptional responses involving extracellular-signal-regulated kinase (ERK) family MAPKs, leading to ATF/CREB transcription factor activation, inducing pro- and anti-inflammatory gene expression [109, 110]. NF-κB in the nucleus induces genes encoding inflammatory-related molecules, including PRRs, chemokines, growth factors, adhesion molecules, cytokines, metalloproteinases, complement factor B, Caspase-11, inhibitors of NF-κB signaling, and more [110].

This complex TLR signaling plays a role in pathogen-triggered inflammation and carcinogenesis. Src kinase Hck is implicated in TLR4-induced TNF-α and IL-6 production [1]. TLR3 signaling can convert tumor-supporting macrophages into tumor suppressors [111]. Understanding these pathways may yield pharmacologic targets against pathogen-associated cancers. Figure 2 illustrates how downstream targets of TLR signaling integrate to induce inflammation.

3.2 TLRs, pathogen-triggered inflammation, and cancer: lessons from microbiota

Toll-Like Receptors (TLRs) are crucial transmembrane proteins containing leucine-rich repeats, pivotal for detecting endogenous danger signals and initiating the early innate immune response against invading pathogens. They primarily sense PAMPs via the MyD88 (myeloid differentiation primary response gene 88) adaptor protein [1, 2]. For example, during *Clostridium difficile* infection, TLR/MyD88 signaling recruits neutrophils and monocytes to the large intestine's lamina propria, preventing the spread of bystander bacteria to deeper tissues. MyD88-deficient mice have significantly increased mortality following *C. difficile* infection [2].

Silencing PRR signaling through loss-of-function studies has shown promise in protecting against chronic inflammatory diseases [112], suggesting that disruptions in microbiota-PRR interactions may promote inflammation. Microbiota translocation from the gut to the systemic circulation can lead to bacterial sepsis [113, 114]. Recent reports highlight the role of small leucine-rich proteoglycans, such as decorin and biglycan, in orchestrating TLR crosstalk during inflammation [115, 116]. In septic inflammation, decorin gene activation and increased plasma levels promote the expression of pro-inflammatory molecules in cancer cells [115].

Recent studies have unveiled two mechanisms by which decorin signaling controls inflammation and tumor growth [115]. First, decorin may act as an endogenous ligand for TLR2 and TLR4, stimulating the production of pro-inflammatory molecules like programmed cell death protein 4 (PDCD4) in macrophages. Second, decorin may prevent translational repression of PDCD4 by reducing the activity of transforming growth factor (TGF)-β1 and the expression of miR-21, a key regulator of oncogenic processes that inhibits PDCD4 translation. This results in a more pro-inflammatory cytokine profile, associated with reduced tumor growth [117].

Experimental evidence underscores the critical role of TLRs in inflammation-mediated carcinogenesis triggered by pathogens. For example, gut-derived LPS can promote hepatocellular carcinoma development by activating TLR4 expression on myeloid-derived immune cells in liver injury models, including those resembling human viral hepatitis. Modulating gut microbiota and TLR4 signaling may offer therapeutic possibilities for hepatitis virus-induced hepatitis treatment and hepatocellular carcinoma prevention [3]. TLR4 signaling also connects chronic pancreatic fibroinflammatory disease with pancreatic carcinogenesis. Inhibiting TLR4 or the MyD88-independent TRIF pathway protects against pancreatic cancer, while MyD88-dependent pathway blockade exacerbates pancreatic inflammation and malignant progression [118].

Bacterial-induced inflammation drives the transition from adenoma to invasive carcinoma in animal models of colitis-associated colorectal cancer. Studies in IL-10 knockout mice exposed to azoxymethane (AOM), a model of colitis-associated colorectal cancer, reveal increased colon tumors when colitis is present [37]. Mice

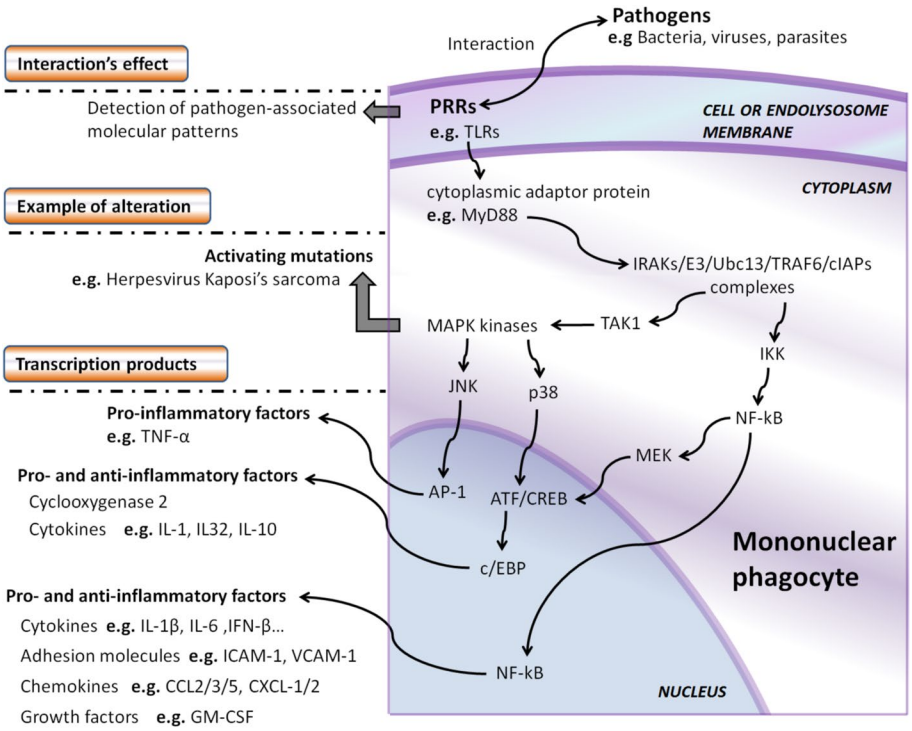

Fig. 2 Toll-like receptor signaling and inflammation. The interactions of pattern recognition receptors (PRRs), like toll-like receptors (TLRs) situated on the cell or endolysosome membranes of mononuclear phagocytes, with pathogen-associated or danger associated molecule patterns trigger both the mitogen associated protein kinase (MAPK) kinase-kinase TAK1 (transforming growth factor-β-activated kinase 1) and the IκB (inhibitor of nuclear factor κB) kinase IKK signaling pathways. These pathways induce the production of either pro-inflammatory factors, or both pro- and anti-inflammatory factors, according to the tissue microenvironment [110], including pro- and anti-inflammatory cytokines, chemoattractant molecules, adhesion molecules, growth factors, other PRR receptors. Activating mutations of the components of these pathways have been reported in various microbe-associated cancers (see text). cIAPs: cellular inhibitors of apoptosis. ERK: extracellular-signal-regulated kinase. E3: ubiquitin E3. IRAKs: interleukin-1 receptor-associated kinases. NF-kB: nuclear factor κB. TRAF6: tumor necrosis factor receptor associated factor 6. Ubc13: ubiquitin-conjugating enzyme E2N

mono-associated with the mildly colitogenic bacterium *Bacteroides vulgatus* show reduced colitis and colorectal tumor incidence, and germ-free AOM-treated IL-10(-/-) mice remain tumor-free. The TLR/MyD88 pathway is essential for microbiota-induced colitis-associated colorectal cancer development, suggesting that intestinal microbiota modulation could reduce cancer risk in inflammatory bowel disease, possibly through probiotics [119]. Infections with *H. pylori* activate oncogenic signaling pathways like Sonic Hedgehog and Wnt, conferring anti-apoptotic effects and stem-like properties to transforming cells in various cancers. In APCMin/+mice, a model of human colon cancer with an APC gene mutation inhibiting Wnt, gut microbiota accelerates tumor growth, possibly through LPS, activating c-Jun/JNK and STAT3 signaling pathways alongside systemic anemia. Infiltrating CD11b+myeloid cells release phosphorylated STAT3 (p-Tyr705) in colonic tumors. These findings illustrate the complex mechanisms behind microbiota bacteria's inflammatory and carcinogenic effects [25, 120–122].

4 Inducible transcription factors, pro-inflammatory cytokines, and cancer

4.1 NF-κB signaling in infection and carcinogenesis

TLR pathways, among others, transmit their signals through NF-κB activation, including pathways involving PRR members NLRs (nucleotide oligomerization domain-like receptors) [110] and C-type lectin receptors [123]. NF-κB activation plays a critical role in human diseases and carcinogenesis. Mutations in NF-κB signaling molecules have been reported in various malignancies. For example, the somatic mutation of TNFAIP3, the gene encoding the deubiquitinating factor A20, is frequent in human B-cell lymphomas, including Epstein-Barr virus-associated AIDS-related lymphoma [35] and Kaposi's sarcoma [124], indicating A20's role as a tumor suppressor in these blood cancers. Additionally, in cancer cells

from adult T-cell leukemia patients, the inhibition of NF-κB-dependent transcriptional activity using the IκB kinase 2 inhibitor IMD-0354 reduced cell survival [67]. Similarly, in Epstein-Barr Virus (EBV)-associated immunoblastic lymphoma, the HIV protease inhibitor ritonavir hindered tumor growth and the infiltration of EBV-positive lymphoblastoid B cells by targeting NF-κB signaling [63]. Kaposi's sarcoma-associated herpesvirus (KSHV) infection has been linked to disease development, along with HIV-1 Tat and herpes simplex virus 1/2 (HSV-1/2) acting as cofactors. HSV-2 infection also activates the NF-κB signaling pathway, suggesting a role in Kaposi's sarcoma pathogenesis. Recent studies in a transgenic model showed that prophylactic IL-15 delivery to mice protected against lethal HSV-2 challenge and metastasis of B16/F10 melanoma cells through NF-κB-dependent induction of the chemokine CCL5 by myeloid immune cells [31]. NF-κB may also bridge chronic inflammation and carcinogenesis in bacterial infection-related cancers such as gastric MALT lymphomas associated with *H. pylori* and Ocular Adnexa MALT lymphomas associated with *Chlamydia psittaci* infection [47].

NF-κB links inflammation to cancer by inducing the production of adhesion molecules, MMPs, COX-2, pro-inflammatory cytokines, and reactive oxygen and nitrogen species [110]. In the normal inflammatory response, NF-κB-induced adhesion molecules, chemokines, and vasomodulatory molecules facilitate immune cell infiltration into infected tissue. However, these processes are also critical in the inflammatory microenvironment of cancer, where adhesion molecules enable tumor cell migration and positioning during metastasis [117]. MMPs aid tumor invasion through their proteolytic activity, while pro-inflammatory and growth factors create a favorable microenvironment for cancer cell survival and proliferation. A feedback loop between pro-inflammatory cytokines like TNF-α and NF-κB activation has been suggested, potentially contributing to constitutive NF-κB activation in inflammatory diseases and its role in linking inflammation and cancer [125, 126].

In squamous epithelium, human keratinocyte proliferation induced by bacterial LPS depends on NF-κB activation and subsequent cyclin D1 up-regulation [127]. NF-κB may also contribute to genomic instability by preventing the elimination of mutated precancerous cells through its antiapoptotic activities and by promoting reactive oxygen species production, potentially causing carcinogenic mutations [92, 128]. In various experimental models where tumor growth was increased by LPS/TLR4 signaling, inhibiting NF-κB signaling in cancer cells with ancient microbial molecules resulted in tumor regression and metastasis regression, highlighting NF-κB as a potential avenue for novel therapies [129, 130].

4.2 Pro-inflammatory cytokines and COX-2 related role in cancer

Inflammation-mediated carcinogenesis triggered by pathogenic microorganisms is associated with several pro-inflammatory cytokines. IL-1, TNF-α, IL-32, IL-23, and IL-6 have been identified as pivotal players. Recent findings indicate that IL-8 and IL-29 can collaborate with the pro-inflammatory factor COX-2 to initiate and sustain infection-related carcinogenesis.

IL-1 and TNF-α released through PRR signaling amplify the inflammatory response via pathways like NF-κB and the oncogenic MAPK. TNF-α mediates its pro-inflammatory effects through TNF receptor 1 (TNFR1), interacting with adaptors like TRADD, RIP1, and TRAF-2. IL-1 triggers IL-1R/MyD88 signaling, critical in cancer development, as seen in studies investigating malignant transformation of keratinocytes [110, 131]. Population-based studies in Argentina and Brazil have linked TNF-α promoter polymorphisms and pro-inflammatory cytokine gene polymorphisms to cervical cancer and gastric cancer risk in H. pylori-infected patients, emphasizing the roles of IL-1β and TNF-α in inflammation-related carcinogenesis [68, 132].

IL-32, overexpressed in inflammatory diseases and gastric cancer, has been investigated in *Helicobacter pylori* infection [133]. IL-32 expression parallels human gastric tissue pathology, and its induction by *H. pylori* is NF-κB-dependent, associated with pro-inflammatory molecules like CXCL1/2 and IL-8. IL-32 also plays a role in hepatitis C virus-related liver inflammation and cancer [134]. IFN-α exerted a significant additive effect on TNF-α-induced but not IL-1β-induced expression of IL-32 in CD14 + monocytes, through a mechanism dependent on both NF-κB and JAK/STAT (Janus kinase/signal transducers and activators of transcription) signaling. These findings highlight IL-32's involvement in infection-triggered inflammation and carcinogenesis in gastric and hepatic tissue, and its potential as a prognostic factor in renal cell carcinoma [135].

Hepatitis B virus (HBV), associated with cirrhosis and hepatocellular carcinoma, induces an inflammation network involving IL-29 (or IFN-λ1), IL-8, and COX-2 [136]. IL-29 inhibits HBV, but IL-8 weakens it, fostering viral persistence. In HBV-infected individuals, IL-29, IL-8, and COX-2 increase. IL-8 also boosts COX-2, while COX-2 limits IL-8, creating a feedback loop. This network may impact HBV-related cancer. Elevated IL-8 levels have been reported in various human cancers, including colon, melanoma, prostate, ovary, and breast cancers, influencing tumor growth, metastasis, and invasion properties [137–141]. COX-2 can be triggered by LPS, pro-inflammatory cytokines (IL-1, TNF-α), and EGF. It produces pro-inflammatory prostaglandins. NSAIDs

reduce cancer risk by modulating COX-2. COX-2 influences cancer by promoting proliferation, antiapoptosis, angiogenesis, and metastasis [142–145]. COX-2's role in inflammation-related cancer is debated. Celecoxib delays esophageal adenocarcinoma progression, while COX-2 overexpression induces bladder cancer. In Barrett's esophagus, COX-2 relates to premalignant cells. In prostate cancer, inflammation upregulates COX-2, promoting angiogenesis [145, 146]. The specific link between microbial-triggered inflammation and cancer via COX-2 requires further study. Arachidonic acids, COX-2 substrates, may also play a role through leukotrienes [147].

5 Oxygen/nitrogen species and microbial-triggered cancer

5.1 Oxidative and nitrative stress

Recent studies strongly indicate that oxidative and nitrative stress play significant roles in inflammation-associated carcinogenesis. Various oxygen and nitrogen compounds have been linked to inflammation-related cancer triggered by microbes. For example, high-risk HPV, the primary cause of cervical cancer, alone doesn't induce tumors, but oxidative stress collaborates with it for carcinogenesis. Dysplastic tissues show oxidative DNA and protein modifications related to cell development, potentially aiding neoplastic progression. Cancer tissues exhibit better control over oxidative damage and reduced carbonyl adducts on detoxifying/pro-survival proteins [148].

Inducible nitric oxide synthase (iNOS), induced by TNF-α, IL-1β, and NF-κB, is overexpressed in chronic inflammatory diseases and various cancers [149, 150]. In liver fluke-induced (*Opisthorchis viverrini*) inflammation, key factors like pro-inflammatory cytokines, NF-κB, COX-2, iNOS, and oxidant/antioxidant balance are disturbed [151]. This results in oxidative and nitrative DNA damage due to excessive reactive oxygen and nitrogen species in inflamed cells. Nitrative DNA damage via NF-κB activation is also reported in urinary bladder cancer caused by *Schistosoma haematobium* infection [152].

Another study [153] revealed that NO from iNOS can induce apoptosis in *H. pylori* through a pERK → pc-Fos/c-Jun → c-Myc → ODC → SMO pathway. Altered L-arginine metabolism due to *H. pylori* arginase and host macrophage arginase II may hinder this process, impacting the host's immune response which indicates possible novel targets for therapeutic intervention in *H. pylori*-associated carcinogenesis.

Enterobacter spp. are linked to solid cancer development [40, 43], and *E. faecalis* produces extracellular superoxide, promoting chromosome instability and colorectal cancer in mice [44]. Antioxidants show promise in sarcoma [154], an HIV-associated malignancy characterized by spindle cell proliferation, inflammatory infiltration, and aberrant angiogenesis caused by KSHV infection. Rac1 expression triggers ROS production and Kaposi's sarcoma-like tumors, making it a potential target [154]. HIF-1, a ROS product, plays a significant role in microbial-triggered carcinogenesis.

5.2 Hypoxia-inducible factor 1

HIF-1, a heterodimeric transcription factor, plays a crucial role in adapting cells to hypoxia by regulating gene expression. It comprises the constitutive subunit HIF-1β and the oxygen-sensitive subunit HIF-1α (or its paralogs, HIF-2α and HIF-3α) [155]. Notably, macrophages utilize glycolysis mediated by HIF-1 for ATP generation even under normoxic conditions, unlike other cell types that rely on this metabolic pathway only during hypoxia [156]. Recent research by Staples et al. [157] highlights that severe hypoxia during monocyte-to-macrophage differentiation, as seen in tumors, wounds, arthritic joints, and inflammation sites, leads to a distinct gene expression pattern in macrophages. This includes up-regulation of HIF-1α mRNA, emphasizing HIF-1's role in chronic inflammation.

Hara et al. [156] reported that deleting the Mint3/Apba3 gene in mice disrupts macrophage functions, increasing resistance to LPS-induced septic shock, suggesting a malfunction in TLR4 response. Interestingly, mutant mice lacking Apba3 showed reduced ATP levels (60% of wild type), affecting ATP-dependent processes like glycolysis, cytokine production, and motility. Understanding APBA3's specific role in macrophages could lead to therapeutics regulating aberrant macrophage function during infection and inflammation, shedding light on septic shock associated with TLR4 inflammatory responses.

HIF-1α is expressed in both acute and chronic inflammation sites [158]. It regulates gene transcription in response to hypoxic stress, growth factors, and plays a role in tumor angiogenesis and growth. Crohn's disease-associated *E. coli* activate HIF-dependent responses, as observed in the inflamed ileal epithelium of Crohn's disease patients, where HIF-1α and CEACAM6 expression coincide [158]. CEACAM6 promotes HIF-1α production and VEGF receptor signaling, suggesting a role for adherent-invasive *E. coli* in gastrointestinal inflammation and neoplastic cell-favoring environments. Targeting HIF-1α could be a viable approach to treating colorectal cancer.

In patients with HPV-associated head and neck squamous cell carcinomas, non-HIF-1 ligand-induced VEGF was associated with a high risk [159], indicating the presence of activating mutations hijacking the HIF-1 receptor signaling pathway. Similarly, HPV type 16 oncoproteins

enhance HIF-1-mediated transcription in non-small cell lung cancer cells [160]. HPV E7 oncoprotein influences HIF-1-mediated transcription by inhibiting histone deacetylases, affecting pro-angiogenic factors in cervical cancer cells [161], suggesting that HPV oncoproteins may create a microenvironment favoring their replication through epigenetic control, including HIF-1.

HCV infection increases the risk of hepatocellular carcinoma [13]. HCV gene expression induces oxidative stress, stabilizing HIF-1α, leading to VEGF release and tumorigenic neovascularization [162]. HIF-1α stabilization activates NF-κB, STAT-3, PI3K/Akt, and p42/44 mitogen-activated protein kinase. HPV-positive tonsillar cancer patients show HIF-1α overexpression [163]. HCV glycoproteins disrupt junction protein expression, enhancing hepatoma migration and expression of tumor growth and metastasis-related genes, including VEGF and TGF-β, regulated by HIF-1α [164]. Kaposi's sarcoma-associated herpesvirus replication is also affected by HIF-1 [165]. Targeting HIF-1 may disrupt oncogenic virus maintenance and suppress carcinogenesis.

HIF-1α is overexpressed in many human cancers [166], making it a potential therapeutic target. Deguelin, a natural compound, inhibits tumor growth and angiogenesis by reducing HIF-1α and its target genes in lung cancer cells [166]. Reovirus infection suppresses HIF-1α in renal carcinoma and colon cancer cells, resulting in apoptosis [167]. Knockdown of HIF-1α inhibits the invasion and growth of hepatocellular carcinoma cells and angiogenesis under hypoxic conditions [168]. Targeting HIF-1 and NF-κB enhances the efficacy of doxorubicin in hepatocellular carcinoma cell lines [169].

6 Concluding remarks

Pathogens entering the body typically induce an inflammatory response, aiming to eliminate them and prevent tissue damage. Evidence from experiments and clinical cases suggests that infectious agents can cause chronic inflammation, contributing to cancer. During this process, immune cells release harmful agents, such as peroxynitrite, superoxide, and MMIF, leading to DNA damage. Excessive production of pro-inflammatory factors, adhesion molecules, and growth factors supports neoplastic cell survival. Various inflammatory signaling pathways like TLR/MyD88, cytokines, NF-κB, and COX-2 play crucial roles in linking pathogen-triggered inflammation to cancer. Targeting these pathways holds promise for therapy. Further research on these connections, especially in microbiota-associated cancers, will deepen our understanding of chronic inflammation's role in cancer development [170–174].

Abbreviations

cIAPs	Cellular inhibitors of apoptosis
ERK	Extracellular-signal-regulated kinase
E3	Ubiquitin E3
IRAKs	Interleukin-1 receptor-associated kinases
NF-kB	Nuclear factor κB
TRAF6	Tumor necrosis factor receptor associated factor 6
Ubc13	Ubiquitin-conjugating enzyme E2N

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