Review Article
The contrasting roles of inflammasomes in cancer

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Abstract: Chronic inflammation plays a decisive role at different stages of cancer development. Inflammasomes are oligomeric protein complexes activated in response to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PAMPs and DAMPs are released from infected cells, tumors and damaged tissues. Inflammasomes activate and release inflammatory cytokines such as IL-1β and IL-18. The various inflammasomes and inflammatory cytokines and chemokines play contrasting roles in cancer development and progression. In this review, we describe the roles of different inflammasomes in lung, breast, gastric, liver, colon, and prostate cancers and in glioblastomas.

Keywords: Inflammasomes, cancer, tumor microenvironment, immune system

Introduction

Inflammasomes are oligomeric protein complexes that are activated upon recognition of diverse pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). They serve as platforms for caspase-1 activation and maturation of inflammatory cytokines, IL-1β and IL-18. Caspase-1-associated cell death or pyroptosis is involved in inflammation and tissue repair [1, 2]. Cleavage of gasdermin D (GSDMD) during pyroptosis [3] promotes the release of IL-1β and IL-18 [4] through the membrane pores [5].

Inflammasomes are classified as canonical and non-canonical types. The canonical inflammasomes include the NLR present in the complex such as the NLRP3-, NLRC4-, NLRP1-, or NLRP6-inflammasome and absent in melanoma 2 (AIM2), one of the PYHIN family members [1]. The non-canonical includes, and a complex that consists of CARD9, Malt1, Bcl-10, caspase-8 and ASC [6]. As shown in Figure 1A, canonical inflammasomes are activated in two steps [7], namely (1) NF-κB mediated transcription of pro-IL-1β and pro-IL-18 upon activation of toll-like receptors (TLRs), NOD1 or NOD2 by DAMPS, PAMPs or tumor necrosis factor-α (TNF-α) [8] and (2) inflammasomes also recognize DAMPS and PAMPs assembled with ASC and recruit procaspase-1 through its N-terminal caspase recruitment (CARD) domain followed by its autocatalytic cleavage. The assembly of different inflammasomes involves distinct proteins. NLRP1 inflammasome is independent of ASC [1]. NLRC4 inflammasomes are assembled when NAIP proteins sense bacterial proteins and recruit NLRC4 [1]. LPS-stimulated CD14 monocytes exhibit a distinct one-step pathway of inflammasome activation by regulating caspases-4 and -5, a process that requires Syk activity and Ca2+ flux [9]. AIM2 inflammasome is activated by binding to double-stranded DNA (dsDNA) resulting in structural changes [1]. However the mechanisms of activation of different inflammasomes by various signals are not fully understood.

As shown in Figure 1B, noncanonical inflammasomes are activated by caspases-8 and -11 [7]. Caspase-11 cleaves gasdermin D and induces pyroptosis and activates IL-1β via NLRP3-dependent caspase-1 activation [10]. Caspase-8 is an IL-1β-converting enzyme during NLRP3 inflammasome activation in caspase1-deficient bone marrow-derived dendritic cells (BMDC) [11], dendritic cells (DCs) [12] and macrophages [13].
Inflammation plays an important role in many cancers. However, the role of inflammasomes in cancers is controversial. This is probably due to heterogeneity of cancer cells and the different cell types associated with cancer such as cancer-associated fibroblasts, tumor-infiltrating immune cells, endothelial cells, adipocytes and pericytes as well as various chemokines and cytokines [14, 15]. Moreover, hypoxic microenvironment in cancer affects the function of inflammasomes in cancer. In this review, we describe the role of different inflammasomes in various malignancies.

Inflammasomes in lung cancer

Lung cancer is the predominant cause of cancer death worldwide with a 5 year survival rate of 16.6% after diagnosis [16]. In non-small-cell lung cancer (NSCLC) patients, serum levels of IL-1β [17] and IL-18 [18] were higher than healthy controls. Moreover, caspase-1, IL-1β, and IL-18 are overexpressed in lung cancer tissues and AIM2 inflammasome is upregulated in NSCLC, whereas high levels of NLRP3 inflammasome are reported in small-cell lung cancer (SCLC) [19]. Therefore, inflammasomes are associated with the biological features of lung cancer. Besides, different inflammasomes are expressed in distinct cell lines and tumor tissues suggesting that their transcription was cell and tissue specific. Therefore, inflammasomes in different subtypes of lung cancer are associated with their histological classification, grading, tumor invasion and chemoresistance [19].

Further, inflammasomes play critical roles in lung cancer. IL-1β represses microRNA-101 (miR-101) expression through the COX2-HIF1α
Immune response to CS involves IL-1 receptor (IL-1R) signaling [33], caspase-1 and P2X7 receptor upregulation and activation [34] and NLRP3/caspase-1 cleavage of IL-1β [35]. Another component of cigarette smoke, α,β-unsaturated aldehyde acrolein represses NF-κB activation, which decreases IL-1β [36]. Besides, inflammasomes also participate in smoke-associated lung carcinogenesis by influencing function of natural killer cells [37]. XWLC-05 lung cancer cell line treated with silica particles secretes IL-1β upregulates enhancer of zeste homolog 2 (EZH2) by downregulating miR-101 and promotes tumor growth and progression [38].

The interaction between the tumor microenvironment and various cytokines and cell types is vital for lung cancer growth and progression. In C57BL/6 mice model with murine Lewis lung carcinoma cell xenograft, secretion of IL-1β from the tumor cells induced abundant vascularization and cytokines such as vascular endothelial growth factor (VEGF), macrophage-inflammatory protein-2 (CXCL2) and hepatocyte growth factor (HGF). This contributes to angiogenesis [39] and chemotactic migration of macrophages [40]. While cultured mouse Lewis lung carcinoma cells do not secrete HGF, coculturing with stromal fibroblasts and tumor infiltrating cells produces HGF [41]. This suggests that the tumor microenvironment as well as stromal fibroblasts and tumor infiltrating cells is crucial in cancer progression.

In the lung metastasis model, IL-1β promotes the metastasis of breast cancer to lungs by increasing the infiltration of myeloid cells such as myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) into the tumor microenvironment [42]. NLRP3 promotes the lung metastasis of melanoma cells by suppressing NK cells [43]. Moreover, in the mouse lung metastasis model, the inhibition of NLRP3 suppresses the metastasis of HCC [44]. NLRP3 also promotes the lung metastasis of breast cancer by increasing lymphangiogenesis [45]. All of these studies provide evidence that inflammasomes promote lung metastasis by releasing inflammatory cytokines and suppressing immune function. As shown in Figure 2, the role of inflammasomes in lung cancer is controversial and the outcomes depend on the type of stimulating factors and inflammasome components involved.
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Breast cancer is the leading cancer diagnosed in women aged 20-45. The breast cancer risk factors include breast density age, family history and expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 [46]. Moreover, inflammasomes play contrasting roles in breast cancer (Figure 3).

The AIM2 inflammasome plays a positive role in breast cancer. In breast cancer cell lines MCF-7 cells, IFNγ induces AIM2 expression that promotes apoptosis through the mitochondrial pathway and the expression of pro-apoptotic proteins, Bad and Bax [47]. AIM2 suppresses human breast cancer cell proliferation and mammary tumor growth in a mouse model by repressing NFkB promoter activity [48]. The NLRP3 inflammasome promotes anti-tumor function by stimulating the dendritic cells to release IL-1β [49]. Different inflammasomes play contrasting roles in breast cancer growth and progression. IL-1β is the main effector of inflammasomes and plays a negative role in breast cancer. Increased serum levels of IL-1β are associated with a high rate of recurrence in breast cancer patients and are critical for tumor growth, angiogenesis, invasiveness, relapse and progression [50-53]. Breast cancer proliferation, migration and invasion are enhanced by the IL-1β /IL-1RI/β-catenin signaling pathway that increase expression of c-MYC, CCDN1, SNAIL1 and MMP2 [54]. IL-1β enhances invasiveness of breast ductal cancer cells by activating ERK1/2 [55]. In the tumor microenvironment, a positive feedback exists where in reduction of IL-1β by metastatic breast cancer cells stimulates MSCs to produce chemokine IL-1β that promote aggressiveness of the breast cancer cells [56].

Adipocytes secrete leptin that promotes breast cancer cell migration and invasion by enhancing the expression and secretion of IL-18 through tumor-associated macrophages (TAMs), which are linked to tumor progression and metastasis [57, 58]. Moreover, IL-18 gene polymorphisms are associated with increased risk of breast cancer [59, 60]. However, multiple studies show that IL-18 plays a positive role in breast cancer therapy. IL-18 overexpressing human mesenchymal stem cells derived from the human umbilical cord (hUMSCs) suppress the proliferation, migration and invasion of breast cancer cells [61, 62]. This contradictory role of IL-18 suggests that the context and cell types that generate IL-18 critically modulate cancer progression. Nearly 15% of all breast carcinomas are triple-negative breast cancer (TNBC) subtype. TNBC is associated with poorer prognosis than other breast cancers because of its aggressive and metastatic behavior [63]. ZER is a sequiterpene isolated from Southeast Asian ginger that suppresses IL1β-induced migration and invasion of TNBC cells.
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Figure 3. Inflammasomes in breast cancer. IL-1β promotes the proliferation, migration, invasion of breast cancer through the secretion of chemokines: VEGF and HGF. Mesenchymal stem cells (MSCs) that are stimulated by IL-1β also produce chemokines: IL-1β. Adipokines promote breast cancer cell migration and invasion by stimulating the expression and secretion of IL-18 in tumor-associated macrophages (TAMs). However, IL-18 overexpressing MSCs generated from human umbilical cord (hUMSCs) suppress the proliferation, migration and invasion of breast cancer cells. AIM2 and ASC also inhibit breast cancer development through promoting apoptosis.

by inhibiting IL-8 and MMP-3 expression [52]. Therefore, ZER is a promising candidate for treatment of triple-negative breast cancer patients.

However, the role of inflammasomes in breast cancer is not clear-cut. Therefore, further investigations are necessary to determine the relationship of inflammasomes like NLRP1 and NLRP6 with breast cancer.

Inflammasomes in gastric cancer

Gastric cancer (GC) is ranked second among all cancer deaths worldwide [64]. Chronic inflammation is one of the main causes of GC. The etiological connection between gastric tumorigenesis and the chronic inflammation is demonstrated by its association with Helicobacter pylori (H. pylori) infection and chronic gastritis. H. pylori infection induces IL-1β and IL-18 expression through TLR-2/NLRP3/caspase-1 axis, which leads to persistent infection and immune tolerance that ultimately progresses to gastric cancer. [65, 66]. This process is also dependent on K⁺ efflux and Ca²⁺ signaling [67]. IL-18 secretion in response to H. pylori infection reprograms the dendritic cells (DCs) into a tolerance-promoting phenotype [68]. THP-1 cells infected by H. pylori also produce IL-1β [69]. H. pylori-induced expression of IL-1β promotes gastric carcinogenesis by upregulating COX-2 expression and repressing acid secretion [70]. Therefore, H. pylori promote gastric inflammation by inducing the secretion of IL-1β and IL-18, which regulate gastric immunity. Hence, elimination of H. pylori infection is critical to prevent gastric cancer. MUC1 is a mucin protein, which is a critical component of the epithelial barrier and protects against H. pylori-induced pathogenesis by inhibiting NLRP3 activation [71]. Withaferin A is a withanolide obtained from Withania somnifera, which inhibits IL-1β production by H. pylori in dendritic cells by inhibiting NLRP3 inflammasomes [72].

There is also increasing evidence that Mycoplasma hyorhinis (M. hyorhinis) plays an important role in many kinds of cancers including gastric cancer. M. hyorhinis-induced NLRP3 inflammasome reduces the release of IL-1β, which promotes gastric cancer metastasis [73].

IL-1β promotes inflammation-induced GC. In the gastric cancer patients, IL-1β levels are significantly higher in the serum and tumor tissues [74, 75]. Moreover, IL-1β levels increase with gastric tumor progression [76]. Hence, IL-1β can be used as a prognostic biomarker. Furthermore, IL-1β gene polymorphisms show synergy with H. pylori infection in gastric cancer development [77-79]. IL-1β inhibits gastric acid secretion, induces epigenetic changes, promotes angiogenesis, mobilizes bone marrow cells and adhesive factors to migrate into the site of tumor and induces releases of other inflammatory factors [76]. IL-1β induces methylation of the E-cadherin, which increases the risk of gastric cancer [80]. These results demonstrate that IL-1β promotes proliferation, invasion and metastasis of gastric cancer cells and also affects the tumor microenvironment.

Many studies have investigated the role of individual inflammasome components in GI cancers. Low caspase-1 expression correlates with stage, lymph node metastasis and survival of gastric cancer patients [81]. In helicobacter infections, caspase-1 regulates the balance
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between Th1 and Th17 cells [82]. ASC/TMS1 mRNA and protein levels are decreased in GC tissues, whereas methylated ASC/TMS1 promoter is an independent prognostic indicator of GC [83].

However, the function of IL-18 and other inflammasomes in GC are not clear and require further investigation.

**Inflammasomes in liver cancer**

In 2008, liver cancer was the fourth most diagnosed cancer in males and seventh in females; it ranked second among males and fifth among females for cancer-related deaths [84]. In 2012, liver cancer was ranked second in cancer-related deaths worldwide [85]. These data reflect the poor prognosis of liver cancer. As shown in Figure 4, the inflammasomes play conflicting roles in liver cancer.

Sex hormones play a protective role in hepatocellular carcinoma (HCC). The 17β-estradiol (E2) decreased HCC progression by increasing NLRP3 inflammasome via E2/ERβ/MAPK signaling pathway [86]. Moreover, NLRP3 inflammasome components are significantly downregulated in human HCC than inflamed and normal hepatic tissues [87]. These studies indicate that the NLRP3 inflammasome plays a positive role in HCC. However, many other studies suggest a contrary role of NLRP3 inflammasome in HCC. In hypoxia, HMGB1 enhances caspase-1, IL-1β and IL-18 levels through NLRP3 and promotes HCC invasion, whereas stable knockdown of HMGB1 suppresses HCC that regulates innate immunity [90]. IL-1β increases major histocompatibility complex class I-related chain A (MICA) levels, which antagonizes NKG2D-mediated immune-surveillance [91].

The major risk factor for HCC is cirrhosis, which is caused by viral infections alcohol and metabolic factors [92, 93]. Inflammasomes are differentially regulated by various hepatitis B virus (HBV) antigens. In chronic hepatitis B (CHB) patients, high AIM2 expression is observed in the high HBV replication group than the low HBV replication group; moreover, high AIM2 levels are positively associated with IL-1β and IL-18 expression in CHB patients [94]. This observation suggests that AIM2 activation may eliminate hepatitis B virus. However, another study demonstrated that AIM2 prevents the recognition of dsDNA expressed by the HBV and therefore assists immune evasion [90]. NLRP3, which is activated by hepatitis C virus (HCV) accumulates in lipid droplets and coordinates with sterol regulatory element-binding proteins (SREBPs) to promote liver disease pathogenesis associated with chronic HCV [95]. In alcoholic liver disease (ALD), NLRP3 plays a protective role, whereas NLRC4 promotes ALD [96]. Ethanol induces the activation of HSCs and promotes production of proinflammatory cytokines such as IL-1β, which contribute to liver fibrosis [97]. IL-1β recruits and activates hepatic iNKT cells that promote liver inflammation and neutrophil infiltration, and induce alcohol-related liver injury [98]. Inflammasomes are also upregulated in the
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non-alcoholic steatohepatitis (NASH) [99]. DAMPs trigger endoplasmic reticulum (ER) stress, which activates inflammasomes leading to inflammation steatosis [100]. Thus, inflammasomes play an important role in the progression of hepatitis. However, the role of other inflammasomes like NLRP1 and NLRC4 requires in-depth investigation.

IL-1β and IL-18 are also important in hepatitis and HCC progression. IL-1β is involved in the pathology of viral fulminant hepatitis [101] and alcoholic steatohepatitis [102]. Hepatic macrophages induced by HCV produce IL-1β through the NLRP3 inflammasome, which contributes to the liver disease [103]. However, there are contrasting reports regarding IL-1β inhibiting HBV infection in liver cells. Watashi et al. reported that priming with IL-1β reduced host cell susceptibility to HBV infection via activation-induced cytidine deaminase (AID) [104] and oxidative stress [105]. HCV-infected monocytes induce IL-18 via inflammasomes that activate NK cells, which produce IFN-γ [106]. However, patients with chronic HCV infection show reduced monocytes function and low IFN-γ levels [106]. This may be due to changes in membrane protein composition on monocytes derived from chronic HCV patients that show depleted levels of IFN-γ due to decreased numbers of CD14+ monocytes [106]. These data show that inflammasomes derived from monocytes, NKS and macrophages perform different functions in hepatitis. Moreover, further investigations are necessary to decipher the roles of NLRP1, NLRP4 and NLRP6 in liver cancer.

Inflammasomes in colorectal cancer

Colorectal cancer (CRC) is one of the major causes of morbidity and mortality in developed countries. Recent data show that the incidence rates of CRC have rapidly increased in China. CRC is frequently associated with inflammatory bowel disease (IBD). Many studies have reported the role of individual inflammasome components in CRC. However, their specific roles may be context dependent. AIM2 reduces Akt activation and tumor burden in murine colorectal cancer models [107]. Reduced AIM2 expression is associated with advanced cancer stages [108] and poor outcomes for CRC patients [109]. However, AIM2 restoration promotes invasiveness in AIM2-deficient colon cancer cells [110]. AIM2-containing microsatellites in the coding region are associated with colorectal cancer progression [111].

NLRP3 induces epithelial-mesenchymal transition (EMT) in colon cancer cells, which contributes to metastasis [112]. Dietary cholesterol promotes AOM-induced colorectal cancer through the activation of NLRP3 by AMPKα/mitochondrial ROS signaling pathway [113]. NLRP3 inflammasome-mediated maturation of IL-1β and IL-18 is necessary for DSS-induced colitis [114]. NLRP3 depletion suppresses colitis [115]. However, some studies show that NLRP3 inflammasome protects against DSS-induced colitis [116] and colitis-associated tumorigenesis in hematopoietic cells [117]. NLRP3 inflammasome promotes IL-18 expression, which suppresses metastatic colorectal cancer growth in the liver by promoting tumoricidal activity of NK cells [89]. This implicates NLRP3 in promoting liver metastasis.

The role of NLRC4 is also controversial. Allen et al. reported that NLRP3−/− rather than NLRP4−/− mice exhibit increased colitis and tumorigenesis [117]. However, Hu et al. reported that Casp1−/− and Nlrc4−/− mice showed greater tumor load than Nlrp3−/− and wild-type mice and NLRC4 expression induces apoptosis and decreases the proliferation of epithelial cells [118]. Meanwhile, NLRC6 activity is necessary to regulate self-renewal of the intestinal epithelium and maintain intestinal homeostasis [119]. NLRC6 is critical in hematopoietic cells for protection against inflammation-related colon tumorigenesis [120]. NLRC6 suppresses tumorigenesis by promoting secretion of IL-18 from epithelial cells [121]. NLRP1 functions similar to NLRC6 in the colon epithelial cell compartment to repress tumorigenesis [122]. Moreover, NLRP1 attenuates CRC through IL-8 and IL-1β, similar to NLRP3 [122]. NLRP12 represses the noncanonical NF-κB pathway through NIK and TRAF3, resulting in suppression of colon inflammation and tumorigenesis [123].

IL-1β promotes CRC cell growth through IL-1β/NF-Kb/miR-181a/PTEN signaling pathway [124]. C5a is involved in colorectal cancer through the IL-β/IL-17A axis through promoting the inflammation and complement-activation product C5a represented a potent inducer for IL-1β in neutrophil [125].
IL-1β promotes tumor growth and invasion by inducing epithelial to mesenchymal transition (EMT) and stem cell phenotype via Zeb1 [126]. In fibroblasts, IL-1β stimulates the production of COX-2, which is a major inflammatory mediator that promotes the proliferation and invasiveness of colon cancer cells [127]. IL-1β produced by neutrophils promotes colitis-associated tumorigenesis through IL-6 [128]. Thus, IL-1β plays a major role in CRC, CRC-associated microenvironment and CRC stem cells. Therefore, IL-1β inhibition is a potential therapeutic strategy to treat CRC. Inositol hexaphosphate inhibits the IL-1β-stimulated colon cancer by degrading MMPs [129].

However, IL-18 plays a tumor-suppressive role in CRC. Eosinophil promote the death of colon cancer cell colo-205 through IL-18 [130]. In Nlrp3 inflammasome-deficient mice, enhanced tumorigenesis is associated with deregulated IL-18 production and increased macrophage infiltration and IL-18-/- mice contained significantly more tumors than those of treated wild-type mice. IL-18 suppresses CRC through release IFN-γ and the IFN-γ promote the production of tumor suppressor STAT1 [131]. Moreover, IL-18 suppresses metastasis of CRC to lung cancer by activating T cells [132] and increasing the number of NK cells [89]. Thus, IL-18 can be used as an effective therapy for CRC.

Extrusion maintains homeostatic epithelial cell numbers and protects against infections. IL-18 secreted by the intestinal epithelial cells upon inflammasome activation recruit immune cells that prevent dissemination of bacteria traversing the epithelium [133, 134]. However extrusion upregulates survival signaling in metastatic tumor cells and helps them to escape from the epithelium [135]. Moreover, persistent IL-18 may play a positive role in colitis [136] and colorectal cancer [137]. These studies demonstrate that extrusion plays a role in epithelium-derived tumor metastasis. However, it is not clear if cancer cells originating from the parenchyma cells induce metastasis through extrusion like hepatocellular carcinoma.

The gut microbiota also regulates susceptibility to multiple human diseases. Changes in intestinal microbial composition are associated with multiple human diseases like IBD and colon cancer [138]. Low fiber diet exacerbates colitis development, whereas very high intake of dietary fiber or short-chain fatty acids (SCFA) acetate protects against colitis by stimulating K+ efflux and hyperpolarization of colonic epithelial cells leading to NLRP3 inflammasome activation [139]. NLRP3 and AIM2 sense the microbial DNA and regulate the gut microbiota, especially in the context of colitis and colorectal cancer [140]. Aim2-/- mice are highly susceptible to colon tumor development and DSS-induced colitis due to perturbations in gut microbiota [141, 142]. The activation of the NLRP6-ASC inflammasome does not change the gut microbiota composition [143]. Thus different inflammasomes play a complex role in CRC, depending on their source, context of cancer development, downstream signaling and gastrointestinal microflora.

**Inflammasomes in prostate cancer**

Prostate cancer is a male-specific cancer that especially affects older men. The initiation of prostate cancer has been linked with multiple factors such as age, race, diet, heredity, and environment [144]. In recent years, there has been a surge in understanding the role of inflammation in prostate cancer.

Hypoxia is a common feature of prostate cancer. Hypoxia contributes to prostate cancer by priming cells for the activation of NLRP3 and AIM2 inflammasomes [145]. Several stimuli such as uric acid crystals, urine reflux, bacteria, or fungi cause injury or infection within the prostate activates inflammasome-mediated proinflammatory cytokines and drive tumor development. For example, Propionibacterium acnes strongly activate inflammasomes in the neutrophils residing in the prostate gland, resulting in prostatitis and prostate cancer [146]. AIM2 inflammasome plays a role in the development of human prostate hyperplasia and prostate cancer [147].

IL-1β and IL-18 serum levels correlate with the risk of carcinoma and the prognosis of established prostate cancer. High serum IL-18 levels have been observed in locally advanced prostate cancer patients [148]. Besides, IL-1β and IL-18 exert immunosuppressive effects and support tumor promoting microenvironment [148]. IL-1β drives prostate cancer progression [149] and also promotes skeletal colonization and progression of metastatic prostate cancer.
cells [150]. Moreover, IL-1β polymorphisms such as IL-1β-511 (rs16944) and IL-1β-31 (rs1143627) are associated with prostate cancer risk [151, 152].

Anakinra, a IL-1 receptor antagonist inhibits both IL-1α and IL-1β and is the most widely used therapeutic agent for prostate cancer [153]. Glucosamine attenuates prostate cancer cell proliferation and migration by targeting IL-1β [154]. Inflammasome-associated studies in prostate cancer require further detailed investigation.

**Inflammasomes in glioblastoma**

Glioblastoma is one of the most aggressive and fatal primary brain tumors in adults. Malignant gliomas are highly invasive with a dismal prognosis despite progress in early diagnosis and aggressive therapeutic interventions [155].

In patients with glioblastoma, the expression of NLRP3 inflammasome predicts poor survival in patients that have undergone radiotherapy [156]. NLRP3 inhibition reduces tumor growth and prolongs the survival of glioblastoma model mice following IR treatment [156]. Caspase-1 is increased in both glioblastoma tissues and glioma cell lines, U87 and T98G, whereas miR-214 inhibits glioblastoma cell proliferation and migration by suppressing caspase-1 [157].

However, the role of IL-1β in regulating glioblastoma progression is still controversial. IL-1β promotes proliferation, migration, and invasion of human glioma cells [158] and increases the cancer stem cell phenotype in murine and human proneural glioma stem cells [159]. IL-1β activates the p38 MAPK pathway and enhances IL-6 that promotes glioblastoma progression [160]. IL-1β also stimulates the secretion of exosomes containing the small heat shock protein, CRYAB that promotes glioblastoma progression [161]. However, IL-1β inhibits the transactivation activity of hypoxia-inducible factor 1 (HIF-1), thereby downregulating adrenomedullin (AM) expression and inducing glioma cell apoptosis [162]. Therefore, cancer microenvironment such as degree of hypoxia can influence cancer outcomes. IL-1β promotes the brain metastasis of breast cancer stem-like cells (CSCs) by activating astrocytes, which are critical for CSC survival [163].

IL-18 plays a controversial role in malignant glioma. IL-18 induces IL-2, which demonstrates significant antitumor activity in glioma models [164]. IL18-expressing BMSCs effectively inhibit intracranial glioma in rats through bone marrow-derived mesenchymal stem cells [165]. In the tumor microenvironment, IL-18 secreted by the microglia promotes migration of glioma cells [166]. However, IL-18 also promotes Fas-mediated apoptosis in Fas-transduced C6 glioma cells [167]. Moreover, IL-18 stimulates macrophages, T lymphocytes and NK cells to produce IFN γ that displays antitumor effects [168]. Moreover, intraperitoneal rIL-18 substantially delays the growth of subcutaneously inoculated gliomas in collaboration with natural killer cells [169].

Hence, different inflammasomes play distinct roles in glioma based on their origin. Moreover, the roles of NLRP1, NLRP6 and AIM2 in glioblastoma are still unknown.

**Crosstalk between exosomes and inflammasomes in cancers**

Exosomes are nano-sized membrane vesicles that are secreted by both normal and cancer cells, which mediate various biological processes such as immune response and tumorigenesis. Inflammasome-derived exosomes directly activate NF-κB signaling pathway in macrophages [170] which promotes gastric cancer progression [171].

AIM2 is activated by dsDNA from dead and cancer cells, which are sensed by AIM2 [1]. Exosomes containing dsDNA from intact lung cancer cells activate AIM2 in adjacent cells, leading to the production of inflammatory cytokines [172]. The pro-inflammatory cytokines and chemokines recruit stromal cells and induce angiogenesis leading to tumor progression [173]. Although chemotherapies are critical for cancer treatment, severe gastrointestinal tract toxicity restricts their application. The cytotoxicity is due to exosomes containing “self-DNA” that activates the AIM2 inflammasome, resulting in secretion of IL-1β and IL-18 that induces intestinal mucositis and late-onset diarrhea [174].

Tumor-derived exosomes serve as vehicles of intercellular communication and are emerging as mediators of tumorigenesis and immune escape. Exosomes from the serum of patients...
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with nasopharyngeal carcinoma (NPC) or the supernatant of TW03 cells increase the production of proinflammatory cytokines such as IL-1β, IL-6, and IL-10, which correlates with advanced lymph node stage and poor prognosis in NPC patients [175].

Liver fibrosis is the main cause of hepatocellular carcinoma. Exosomes derived from CCl4-treated hepatocytes induce the expression of IL-1β and IL-23 in HSCs [176] and contribute to liver fibrosis. In non-alcoholic steatohepatitis (NASH), lipids induce release of hepatocyte exosomes, which activates the macrophages that release IL-1β and IL-6 [177].

These studies indicate that exosomes serve as vehicles to activate inflammasomes and promote the production of inflammatory factors, which are critical for tumor progression. However, the connection of exosomes and NLRP1, NLRP3, NLRP6 inflammasomes is unknown. Moreover, it is unclear if exosomes containing inflammasomes form a metastasis niche. More investigations are necessary to unravel these unanswered questions.

Perspectives

In recent years, the complex roles of activated inflammasomes have gained attention in cancer development and therapy. Many factors trigger activation of inflammasomes. Moreover, different inflammasomes play diverse roles within the same tissue. Therefore, given their complex roles, it is important to explore their function in context of tissue or cell specificity and cancer stages. Compounds that target inflammasomes such as IL-1β neutralizing antibodies and IL-18 binding protein have been developed. However, their clinical application in cancer therapy needs to be determined. In the future, the mechanism of the activation of the various inflammasomes and their effect on the immune system needs to be addressed in greater detail. The various signaling mechanisms that regulate the activation of different inflammasomes also need to be defined in greater detail. While pyroptosis is vital in anti-cancer treatment, oxidative stress, mitochondrial dysfunction and release of inflammatory factors are also involved in carcinogenesis. Therefore, their role in tumor cell apoptosis, necrosis and ferroptosis needs to be explored.

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None.

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