Cancer Immunology Research

Inflammasomes and Cancer

Rajendra Karki, Si Ming Man, and Thirumala-Devi Kanneganti

Abstract

Inflammation affects all stages of tumorigenesis. A key signaling pathway leading to acute and chronic inflammation is through activation of the caspase-1 inflammasome. Inflammasome complexes are assembled on activation of certain nucleotide-binding domain, leucine-rich repeat–containing proteins (NLR), AIM2-like receptors, or pyrin. Of these, NLRP1, NLRP3, NLRC4, NLRP6, and AIM2 influence the pathogenesis of cancer by modulating innate and adaptive immune responses, cell death, proliferation, and/or the gut microbiota. Activation of the inflammasome and IL18 signaling pathways is largely protective in colitis-associated colorectal cancer, whereas excessive inflammation driven by the inflammasome or the IL1 signaling pathways promotes breast cancer, fibrosarcoma, gastric carcinoma, and lung metastasis in a context-dependent manner. The clinical relevance of inflammasomes in multiple forms of cancer highlights their therapeutic promise as molecular targets. In this review, we explore the crossroads between inflammasomes and the development of various tumors and discuss possible therapeutic values in targeting the inflammasome for the prevention and treatment of cancer. *Cancer Immunol Res; 5(2); 94–99. ©2017 AACR.*

Introduction

Inflammation triggered by microbial or danger signals drives many forms of cancer in humans (1). Inflammation associated with tumor development is triggered by a variety of immune cells, including macrophages, neutrophils, dendritic cells, natural killer (NK) cells, and T and B lymphocytes (2). A central mechanism driving inflammation in immune cells is orchestrated by the inflammasome, a cytoplasmic multimeric protein complex that provides a molecular platform for activation of the cysteine protease caspase-1 (3). Activated caspase-1 mediates proteolytic cleavage and release of the proinflammatory cytokines IL1β and IL18 and initiates an inflammatory form of programed cell death known as pyroptosis (3).

Certain members of the nucleotide-binding domain, leucine-rich repeat containing proteins (NLR) and AIM2-like receptors (ALR), form inflammasome complexes in response to pathogen-associated molecular patterns (PAMP) or danger-associated molecular patterns (DAMP; ref. 3). Mutations in genes encoding inflammasome components often lead to susceptibilities to cancer, infection, and autoinflammatory diseases in humans. In the context of cancer, polymorphisms in the gene encoding NLRP1 are linked to mesothelioma (4), melanoma (5), and epidermal hyperplasia (6); those of NLRP3 are associated with melanoma (5) and colorectal cancer (7); and those of AIM2 with colorectal cancer (8). Furthermore, our contemporary appreciation of the functional importance of inflammasomes in cancer is illuminated by mouse models. Here, we highlight recent development in our understanding of inflammasomes in cancer and outline the therapeutic potential of modulating inflammasome responses for use in anticancer therapies.

Protective Roles of Inflammasomes in Cancer

The global inflammasome-initiating sensor of PAMPs and DAMPs, NLRP3, assembles a fully functional inflammasome complex by recruiting the inflammasome adaptor protein, ASC, and the cysteine protease, caspase-1. The ability of NLRP3 to respond a variety of signals contributes to its biological importance in a number of diseases, including colorectal cancer, melanoma, and transplantable tumors. Multiple studies have shown that mice lacking NLRP3 are hypersusceptible to colitis and colitis-associated colorectal cancer induced by the DNA damaging agent azoxymethane (AOM) and chemical colitogen dextran sulfate sodium (DSS; refs. 9–12). However, another study has suggested that mice lacking NLRP3 are more resistant to DSS-induced colitis compared with wild-type mice (13), whereas a further study has found a similar tumor burden between wild-type mice and mice lacking NLRP3, treated with AOM and DSS (14). It is possible that alteration in the gut microbiota between different animal facilities could have contributed to the differences observed in these studies. It is important to note that mice lacking ASC and caspase-1 are also susceptible to DSS-induced colitis and colitis-associated colorectal cancer (9–11, 15), providing substantial evidence to favor a protective role of inflammasomes in an inflammatory model of colorectal cancer.

Bone marrow chimera studies have identified that signaling through the NLRP3 inflammasome in the hematopoietic, but not in the stromal, compartment is essential for mediating protection against tumorigenesis (9, 10). The ability of inflammasome sensors such as NLRP3 to mediate secretion of IL18, a cytokine that contributes to epithelial barrier repair against damage, is a potential mechanism explaining the protective role of IL18 against colitis-associated colorectal cancer (Fig. 1A; refs. 5, 6,

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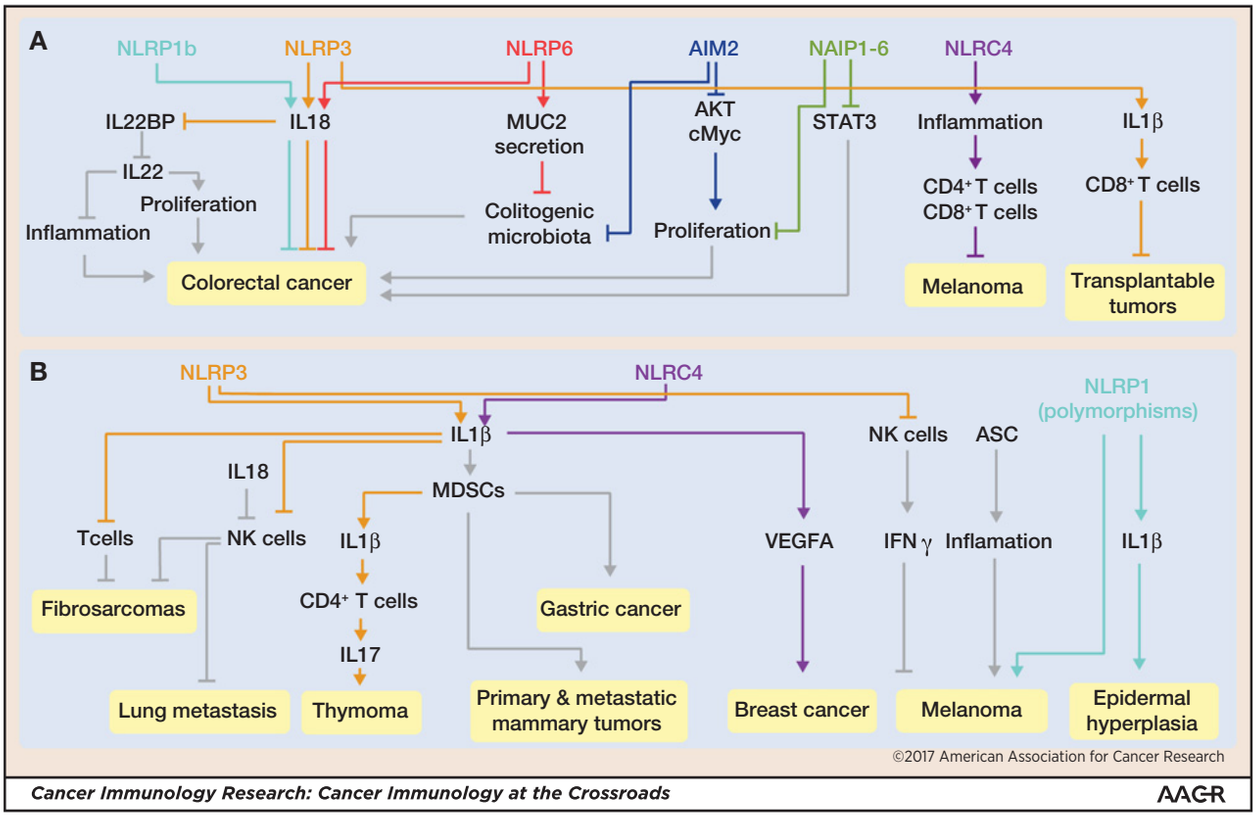

Figure 1.

Diverse roles of inflammasome sensors in tumorigenesis. **A,** NLRP1b, NLRP3, and NLRP6 mediate the production of IL18, contributing to the protection against colitis-associated colorectal cancer. The IL18 axis can also induce tumoricidal activity of NK cells against metastasized colonic tumor cells, downregulate IL22 binding protein (IL22BP), and inhibit the colonization of colitogenic microbiota, possibly through its role in MUC2 secretion by goblet cells. The NLRP3 inflammasome and the IL1β–IL1 receptor (IL1R) signaling axis drives a T-cell response toward transplantable tumor cells. Mouse NAIP1–6 proteins control phosphorylation of STAT3 and the expression of genes encoding antiapoptotic and proliferation-related molecules. NLRC4 controls the suppression of melanoma growth by amplifying inflammation in macrophages and potentiates production of IFNγ in T cells. AIM2 inhibits phosphorylation of AKT and cMyc activities and stem cell proliferation, while preventing colonization of colitogenic microbiota. **B,** The NLRP3–IL1β–IL1R signaling axis suppresses the tumoricidal activity of NK cells and T cells and promotes methylcholanthrene (MCA)-induced fibrosarcomas. It also induces secretion of IL17 by $CD4^+$ T cells and dampens the antitumor efficacy of chemotherapeutic agents in thymoma. Overexpression of IL1β mobilizes myeloid-derived suppressor cells (MDSC) to the stomach and induces gastric cancer. IL1 signaling drives accumulation of MDSCs and promotes primary and metastatic mammary tumors. Inflammasome-independent activity of NLRP3 suppresses NK cells and increases lung metastasis in certain models of melanoma. The NLRC4 inflammasome mediates expression of adipocyte-mediated vascular endothelial growth factor A (VEGFA) and accelerates the progression of breast cancer. In some cases, ASC increases the viability and growth of melanoma cells and promotes inflammation in infiltrating myeloid cells and the development of skin cancer. Mutations in the gene encoding NLRP1 are linked to melanoma and epidermal hyperplasia in humans.

9–11, 15–38). In contrast with previous studies showing that mice lacking IL18 are susceptible to DSS-induced intestinal inflammation and tumorigenesis (9, 16, 17), a study has found that mice with a conditional deletion of IL18 in either epithelial cells or hematopoietic cells are more resistant to DSS-induced colitis compared with cohoused wild-type mice, indicating an IL18-dependent function in both enterocytes and hematopoietic cells (39). Under cohousing conditions whereby mice harbor a similar microbiota profile, IL18 inhibits goblet cell maturation prior to the onset of colitis to drive pathology (39). However, injection of recombinant IL18 into mice lacking inflammasome components reduces the prevalence of tumors in response to AOM and DSS (9), suggesting that this inflammasome-associated cytokine could be considered a potential candidate in immunotherapy against certain cases of colorectal cancer.

NLRP3 inflammasome-mediated secretion of IL18 can also induce tumoricidal activity of NK cells against metastasized colonic tumor cells in the mouse liver (19). In addition, IL18 promotes downregulation of the soluble IL22 receptor, IL22-binding protein (IL22BP; ref. 24; Fig. 1A). Controlled production of IL22BP fine-tunes the biological activity of IL22, a cytokine that exerts protective effects against intestinal damage at the peak of inflammation and promotes tumor development at later stages (24). IL22 also maintains IL18 expression in epithelial cells of the ileum, whereas IL18 itself is required for IL22 expression in $CD4^+$ T cells and innate lymphoid cells (40).

The diametrical roles of IL18 have also been observed in lung metastasis. Recombinant IL18 injected into mice twice within a week enhances the development of B16F10 metastases, whereas daily administration for 5 days reduces tumorigenesis (41). In

addition, mice lacking IL18 are more susceptible to B16-F10 tumor metastasis (28). It is possible to speculate that temporary exposure to IL18 might drive inflammation and accelerate metastasis, whereas a sustained circuit of IL18 might be fully required to enhance and shape antitumor immunosurveillance. Indeed, IL18 has the capacity to fine-tune the activation status of NK cells (28, 41). In cases in which IL18 is detrimental, the use of IL18 binding protein (IL18BP, a soluble protein that binds to IL18) to neutralize IL18 might be beneficial in the treatment of certain types of cancer (Fig. 2; refs. 3, 41–51).

The NLRP3 inflammasome is also required for anticancer adaptive immune responses. The release of ATP by dying tumor cells treated with chemotherapeutic agents activates the NLRP3 inflammasome and the IL1β–IL1 receptor (IL1R) signaling axis in dendritic cells (ref. 25; Fig. 1A). This pathway drives an effective $CD8^+$ T-cell response toward transplantable tumor cells (25). As a result, oxaliplatin therapy of transplantable tumors in mice lacking the NLRP3 inflammasome is ineffective because IL1 production from dendritic cells is not induced, nor are $CD8^+$ T cells primed (25).

In addition to NLRP3, other NLR sensors, including NLRP1b and NLRP6, mediate protection against tumorigenesis (18, 20–23, 52; Fig. 1A). In mice, the NLRP1b inflammasome provides protection against colon tumorigenesis, mediating secretion of both IL1β and IL18 in stromal cells of the colon (18). NLRP6 has several interrelated mechanistic functions by which it confers protection against colon tumorigenesis in mice. NLRP6 has been proposed to activate caspase-1 and drive IL18 production in the intestine in response to AOM and DSS treatment (20–22). The NLRP6–IL18 signaling axis prevents the colonization of procolitogenic bacterial species TM7 and those of the *Prevotellaceae* family (21). Furthermore, NLRP6 is essential for MUC2 secretion by goblet cells to clear potentially colitogenic bacteria (23, 26). NLRP6–dependent secretion of MUC2 in the intestinal epithelium have been shown to be dependent and independent of the inflammasome (23, 26), observations that could be attributed to differences in the gut microbiota and the mouse facilities housing the animals.

The ability of inflammasome sensors to provide protection against cancer does not always rely on the effector functions of caspase-1 and the cytokines processed by inflammasomes (Fig. 1A). Mouse NAIP1–6 proteins are components of the NLRC4 inflammasome and have been linked to the protection against AOM-DSS–induced colorectal cancer (27). The mechanism

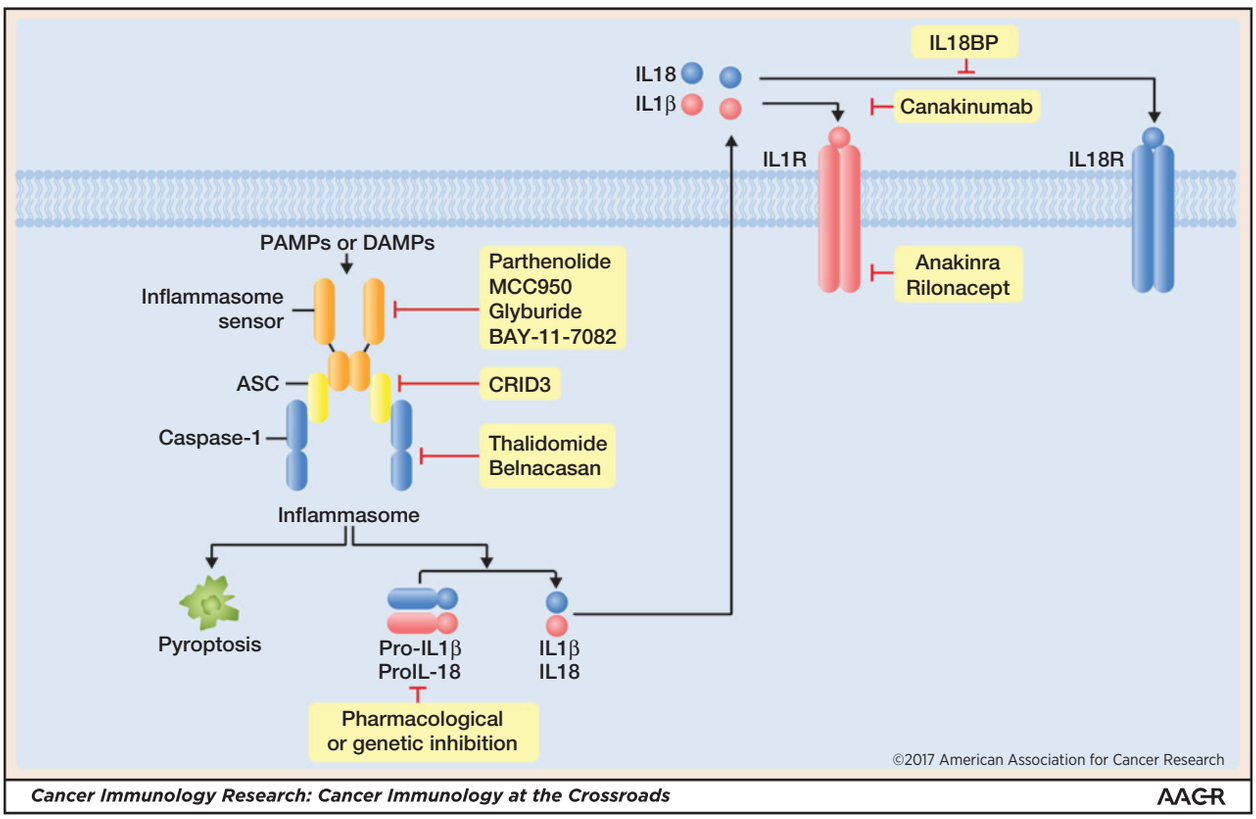

Figure 2.
Therapeutic targets of the inflammasome pathway. Recognition of pathogen-associated molecular patterns (PAMP) or danger-associated molecular patterns (DAMP) by inflammasome-initiating sensors leads to the activation of the inflammasome and initiation of pyroptosis and release of the bioactive form of IL1β and IL18. IL1β and IL18 engage in autocrine and paracrine signaling pathways via the IL1 receptor (IL1R) and IL18 receptor (IL18R), respectively. The inflammasome signaling pathway can be inhibited by pharmacologic inhibition of activation of the inflammasome (parthenolide, MCC950, glyburide, and BAY-11-7082), ASC oligomerization (CRID3), caspase-1 (thalidomide and belnacasan or VX-765), and IL1R (anakinra or kineret, and rilonacept or arcalyst), or neutralizing IL1β (canakinumab or ilaris) or IL18 (IL18 binding proteins or IL18BP).

driving this response is independent of the NLRC4 inflammasome, but relates to the ability of NAIP proteins to inhibit hyperactivation of the transcription factor STAT3 and the expression of genes encoding antiapoptotic and proliferation-related molecules (27). Further, some evidence suggests that adjuvant-based cancer immunotherapies targeting cytosolic NAIP proteins and surface-associated TLR5 could be beneficial. The NAIP proteins and TLR5 both recognize flagellin of certain bacteria (3). Enforced expression of flagellin in tumor cell lines, ensuring dual recognition by NAIP proteins and TLR5, induces tumor cell clearance by innate immune cells and activation of tumor-specific $CD4^+$ and $CD8^+$ T-cell responses in mice (53). These findings suggest that recognition of tumor cells by the inflammasome and other innate immune sensors could lead to desirable outcomes.

The role of NLRC4 itself in the AOM-DSS–induced tumor model is unclear; a study suggests that NLRC4 prevents colorectal tumorigenesis by inhibiting cellular proliferation and driving cell death (14), whereas another found no role for NLRC4 (10). NLRC4 can also amplify inflammatory signaling pathways in macrophages independently of inflammasome assembly and potentiates production of IFNγ in $CD4^+$ and $CD8^+$ T cells to dampen melanoma tumor growth in mice (29).

In addition to NLRs, the DNA-sensing inflammasome sensor AIM2 can inhibit AOM-DSS–induced and spontaneous colorectal tumorigenesis via an inflammasome-independent mechanism (refs. 30, 31; Fig. 1A). AIM2 inhibits overt proliferation of intestinal stem cells and promotes cell death (30). Furthermore, AIM2 interacts with and limits the activation of DNA-dependent protein kinase (DNA-PK) to reduce phosphorylation of AKT, which governs cell proliferation (31). In addition, AIM2 expression prevents colonization of colitogenic microbiota and reduces susceptibility of mice to colorectal tumorigenesis (30). Overall, substantial evidence suggests that inflammasome sensors have tumor-suppressive roles in certain forms of cancer. These oncogenic inhibitory activities are dependent on the ability of inflammasome sensors to modulate cytokine production, engaging T-cell activities, cellular proliferation, and maturation, and the microbiota profile of the host (Fig. 1A).

Detrimental Roles of Inflammasomes in Cancer

Activation of the inflammasome leads to inflammatory responses and, in some cases, suppression of antitumor immunity (Fig. 1B). NLRP3 activity is associated with increased lung metastasis when mice were injected intravenously, but not subcutaneously, with B16-F10 melanoma cells or RM-1 prostate carcinoma cells (28, 32). In this case, mice lacking NLRP3 have a substantially reduced number of lung metastases compared with wild-type mice, whereas mice lacking caspase-1 and caspase-11 or IL1R have a similar number of lung metastases compared with wild-type mice (28). The negative effect of NLRP3 is also observed when mice are vaccinated with wild-type dendritic cells pulsed with B16-F10 melanoma cell lysates prior to injection with B16-F10 melanoma, such that a greater proportion of vaccinated mice lacking NLRP3 survived compared with that of vaccinated wild-type mice (32). The deleterious effect of NLRP3 in the melanoma model is owing to its ability to suppress activation of NK cells that secrete IFNγ and kill tumor cells (ref. 28; Fig. 1B).

The inflammasome adaptor protein ASC also appears to have multiple biological activities that affect the outcome of tumorigenesis (34). A knockdown of the gene encoding ASC increases the viability and growth of primary melanoma cells, whereas it reduces the viability and growth of metastatic melanoma cells, when these cells were injected into nude mice (34). Using cell-type–specific knockout mouse strains lacking ASC in a chemically induced skin carcinogenesis model, ASC was found to limit keratinocyte proliferation and tumor formation, whereas it promotes inflammation in infiltrating myeloid cells and the development of tumors (ref. 35; Fig. 1B). These findings further highlight the cell-type and tissue-specific roles for inflammasome components in cancer.

In addition to IL18, activation of the inflammasome leads to secretion of the inflammasome substrate IL1β. IL1β is involved in the pathogenesis of spontaneous gastric cancer or *Helicobacter felis*-induced gastric cancer (33). A transgenic mouse strain engineered to overexpress human IL1β in the stomach is prone to developing gastric cancer due to increased mobilization of myeloid-derived suppressor cells (MDSC) to the stomach (33). A deleterious role for IL1 signaling is also supported by the finding that mice lacking IL1R have a delayed accumulation of MDSCs and reduced primary and metastatic mammary tumors (36), suggesting that inflammation driven by the IL1R signaling pathway is detrimental (Fig. 1B).

The relationship between IL1R signaling and MDSCs in cancer is further demonstrated in a study showing that activation of the NLRP3 inflammasome by chemotherapeutic agents gemcitabine and 5-fluorouracil leads to IL1β production in MDSCs (37). Production of IL1β by MDSCs induces secretion of IL17 by $CD4^+$ T cells and dampens the antitumor efficacy of gemcitabine and 5-fluorouracil (37). The IL1β–IL1R signaling axis activated by the NLRP3 inflammasome has an adverse role in methylcholanthrene (MCA)-induced fibrosarcomas (28). In this case, IL1β suppresses the tumoricidal activity of NK cells and T cells (28). Moreover, IL1β produced as a result of activation of the NLRC4 inflammasome mediates expression of adipocyte-mediated vascular endothelial growth factor A and angiogenesis, which accelerates the progression of breast cancer (38). Gain-of-function mutations in the gene encoding NLRP1 induce spontaneous inflammasome activation and IL1 production and drives epidermal hyperplasia in humans (ref. 6; Fig. 1B).

Owing to the detrimental effects of the IL1R signaling pathway, treatment of mice with IL1R antagonist IL1Ra enhances the antitumor effect of gemcitabine and 5-fluorouracil (37). In addition, neutralizing IL1β or IL1R at early stages of tumorigenesis reduces the incidence of MCA-induced fibrosarcomas in mice (28). Inhibitors of IL1 cytokines, such as Anakinra, have been suggested for use in prophylaxis or treatment of multiple myeloma (ref. 48; Fig. 2). Similarly, thalidomide, an immunomodulator approved by the FDA can inhibit caspase-1 activation and is used for the treatment of malignant myeloma (ref. 46; Fig. 2). Excessive inflammation induced by inflammasome activation and inflammasome substrates is a consistent theme that seems to explain the detrimental effects of inflammasomes in multiple forms of cancer. The complex and diametrical roles of inflammasome components in different forms of cancer suggest that anticancer therapies must be tailored to the specific cancer type and stage of disease.

Conclusions

In this review, we provided a brief overview of the biological importance of inflammasomes in different forms of cancer. Activation of inflammasome sensors is largely beneficial in colitis-associated colorectal cancer largely owing to the epithelial healing effects of the IL18 signaling pathway, regulation of cellular proliferation, maturation and cell death, and maintenance of a healthy gut microbiota. Identification of novel tumor-suppressive mechanisms of inflammasome sensors pushes the boundaries of the traditional roles of inflammasomes.

In other cases, inflammation triggered by inflammasomes and IL1 signaling leads to suppression of antitumor immunity conferred by NK cells and T cells that is detrimental to the development of fibrosarcoma, melanoma, gastric carcinoma, and lung metastasis. As a result, boosting or reducing the activity of inflammasomes or their effector molecules could be efficacious by tailoring therapy to specific types of cancer. Several small molecules, antagonists, and monoclonal antibodies are being developed against components of the inflammasome for use in therapies to control cancer (Fig. 2). However, inappropriate use of inflammasome modulatory therapies might lead to suppression of antitumor immunity and/or increased susceptibility to infection and the development of metabolic and autoinflammatory diseases.

Because inflammasome sensors regulate multiple signaling pathways beyond that of caspase-1, an understanding of which molecular mechanism is governed by inflammasome components in specific tumors is essential. The protumorigenic and antitumorigenic properties of inflammasomes are largely determined by the types of cells, tissues, and organs involved. The use of tissue- and cell-type–specific conditional deletion approaches in mice would fully reveal the complex functions of inflammasomes in the progression of cancer. The biological relationship between inflammasomes and cancer provides promising avenues with which to explore new anticancer therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R. Karki, S.M. Man, T.-D. Kanneganti
Writing, review, and/or revision of the manuscript: R. Karki, S.M. Man, T.-D. Kanneganti

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