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Review article

Inflammasome as a promising therapeutic target for cancer

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ABSTRACT

Inflammasomes are the major mechanistic complexes that include members of the NOD-like receptor (NLRs) or AIM2-like receptors (ALRs) families, which are affiliated with the innate immune system. Once NLRs or ALRs are activated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), the caspase-1 or -11 is activated by binding with NLRs or ALRs via its own unique cytosolic domains. As a result, caspase-1 or -11 enhances the production of IL-1β and IL-18, which results in inflammation via the recruitment of immune cells, such as macrophages, and the promotion of programmed cell death mechanisms such as pyroptosis. In addition, the consistent cascades of inflammasomes would precede both minor and severe autoimmune diseases and cancers. The clinical relevance of inflammasomes in multiple forms of cancer highlights their therapeutic promise as molecular targets. To closely analyze the physiological roles of inflammasomes in cancers, here, we describe the fundamental knowledge regarding the current issues of inflammasomes in relevant cancers, and discuss possible therapeutic values in targeting these inflammasomes for the prevention and treatment of cancer.

1. Introduction

Sophisticated immune system network is present throughout the bodies of most invertebrates to allow for the efficient recognition of a number of pathogens. In short, physical barriers such as the skin, epithelial cells, and probiotics, which are called the primary protective immune system, prevent foreign antigens from invading cells. If the antigens pass through the primary immune defense barrier, pattern-recognition receptors (PRRs) recognize them as conserved molecules of microorganisms, which are termed pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), and then, the cascades of immune responses are expanded [1]. Membrane receptors such as Toll-like receptors (TLRs) become aware of PAMPs or DAMPs, and send signals to nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and absent in melanoma 2 (AIM2)-like receptors (ALRs) or other molecules that activate the PRRs in the cytosol of the host cell. Afterward, they combine via their homologous components and form a large protein complex called an 'inflammasome' [2]. Inflammasomes are key structures that are critical to the host defense mechanism, and disrupted inflammasome activation is involved in the development of various human diseases including autoimmune diseases, cancers, and neurological disorders. Actually, the mutations on the genes for NLRP1, NLRP3, NLRC4, and AIM2 are related to the development of various cancers such as mesothelioma, melanoma, colorectal cancer, and epidermal hyperplasia [3–6]. Therefore, the controlled mechanism of inflammasome formation enables to circumvention of the onset of physiological diseases [7]. In this review, we discuss the roles of inflammasomes in tumor progression and the latest developments regarding the current inhibitors that regulate the activation of inflammasome signaling for effective cancer therapy.

2. Inflammasomes

The inflammasome is a multiple protein complex formed in the cytoplasm through the binding of bacterial, viral or host danger signals to the NLR receptor followed by the activation of caspase-1, which is required for the production of IL-1β. It was first reported that the

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inflammasome is associated with gout development through of oligomerization and the activation of caspase-1 [8].

NLRs and ALRs are subunits of PRRs and are important elements of the inflammasome complex, which is a component of the innate immune system and an intracellular detector of foreign materials [2,9,10,8]. The currently well-known inflammasomes are NLRP1, NLRP3, NLRC4, and AIM2, as well as pyrin [2,11]. Others include NLRP2, NLRP6, NLRP7, NLRP12, and ALR protein IFI16, but these inflammasomes still need to be studied to identify their exact mechanisms [7]. The inflammasome is a large molecule unit formed via the collection of homologous proteins that belong to the subunits of PRRs [12]. PRRs are receptors that recognize foreign molecules in the cell membrane or cytosol, and are composed of TLRs, NLRs, and C-type lectin-like receptors (CTLRs) [12]. Among these subunits, the main PRRs that form the inflammasome are members of the NLR family [2]. There are additional family members, such as NLRP2 and NLRP7, that have recently been discovered, but these are still need to be confirmed [2].

The NLR family contains the nucleotide-binding domain (NBD) and the leucine repeat protein (LRR), which differentiate this family from other inflammasomes [13] (Fig. 1). NLRPs associate with ASC (apoptosis-associated speck-like protein contains CARD), which contains two basic domains such as caspase activation and recruitment domain (CARD), and the pyrin domain (PYD). NLRC also contains the PYD [13]. ASC contains CARD and PYD domains, helping PRRs to form the inflammasome, and ASC deficiency can cause several diseases, and bring the unnecessary activation of inflammasomes [11,14]. Caspase-1 consists of two heterodimers of p20 and p10 subunits, as well as a CARD domain that binds with CARD-containing proteins such as ASC or NLRC (Broz and Dixit). AIM2 contains a PYD domain corresponding to NLRP and a hematopoietic IFN-inducible nuclear protein with a 200-amino acid repeat (HIN200) domain that recognizes foreign dsDNA [14]. With the exception of these two PRRs, there are two other proteins, ASC and caspase-1, which are associated with the formation of inflammasome complexes. Although the components of inflammasomes have structural similarities, they never recognize the same external stimuli. For example, NLRP1 responds to muramyl dipeptide (MDP) instead of mycobacteria or peptidoglycan, and induces cellular immunity. NLRP3 responds to PAMPs and DAMPs derived from cell debris. NLRC4 reacts with flagellin and the bacterial type III secretion system (T3SS). Likewise, AIM2 responds to dsDNA [7,10]. Procaspase1 binds with NLR or ASC, and activates itself by means of auto-cleavage to form activated caspase-1.

Furthermore, activated caspase-1 allows pro-IL-1β and pro-IL-18 to convert into IL-1β and IL-18, respectively, and initiates programmed cell death via specific mechanisms such as pyroptosis or necroptosis (Fig. 1) [7,10]. Pyroptosis is induced by the cleavage of gasdermin D, and its N-terminus fragment can form the pores on lipid membranes as well as trigger the rupture and swelling of cells [15]. As a result, pyroptosis enhances the production of the PAMPs and DAMPs involved in the inflammatory microenvironment, which eventually stimulates the progression of cancer metastasis. Moreover, inflammasome activation might be involved in necroptosis, which is a regulated cell death (RCD) process indicating a programmed form of necrosis, or inflammatory cell death [16].

Released IL-1β and IL-18 trigger the differentiation of inflammatory

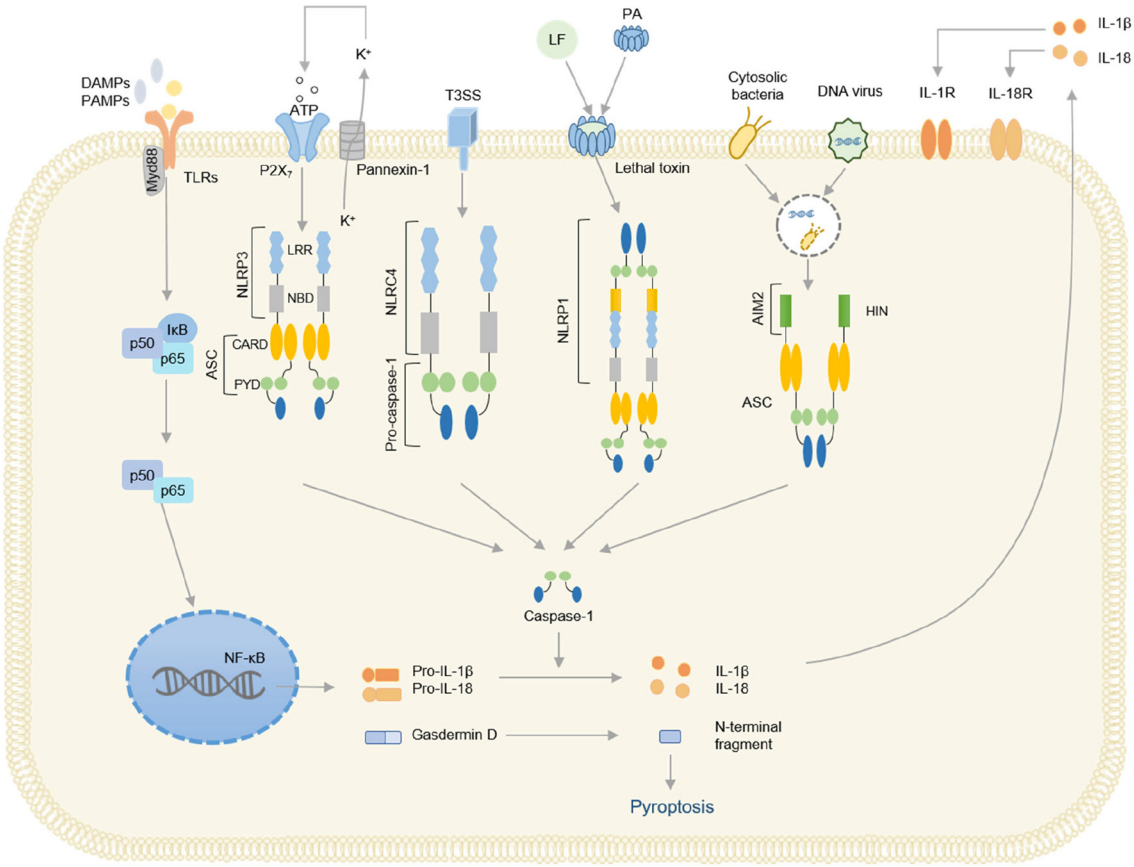

Fig. 1. Scheme of the inflammasome activation.
As the priming activation step, TLRs are phosphorylated by the exposure to PAMPs or DAMPs, and successively activate NF-κB. Subsequently, NF-κB stimulates the transcription of inactive NLRP3, pro-IL-1β, and pro-IL-18 as inactive. The consequent stimulation of the NLRPs and AIM2 inflammasome enables the oligomerization of inactive NLRPs or AIM2, ASC, and procaspase-1. The inflammasomes catalyze the conversion of procaspase-1 to caspase-1, resulting in the production and secretion of the mature IL-1β and IL-18.

cells, which in turn can induce an autoimmune responses or tumor progression [17]. IL-18 belongs to the IL-1 family and regulates innate and adaptive immune responses through the direct recruitment or differentiation of various types of immune cells including natural killer (NK) cells, monocytes, dendritic cells, T cells, and neutrophils. IL-18 enhances the cytotoxicity and production of IFN-γ by neutrophils and NK cells, and the phagocytosis and cytokine production by macrophages [17]. In the immune response to pathogen infections, myeloid cells and, in particular, macrophages, are a major cell source of inflammasome activation and IL-1β production. Myeloid cell is an important component of the tumor microenvironments, and has been implicated in tumor growth and progression, as well as poor cancer prognosis. Myeloid cells that have infiltrated into tumor tissues are composed of heterogeneous populations, primarily $CD11b^+Gr1^+$ granulocytes, also referred to as myeloid-derived suppressor cells (MDSCs), and $F4/80^+ARG1^+CD169^+$ tumor-associated macrophages (TAMs) [18,19]. However, the number of myeloid cells is increased significantly in tumor tissues of tumor-bearing mice or human cancer patients [18,19].

2.1. Types of inflammasomes

2.1.1. NLRP1 inflammasome

The first discovered inflammasome family was the NLRP1 family, which was identified in humans before being recognized in murine models [9,10]. NLRP1 consists of caspase-1, caspase-5, ASC, and a triphosphate ribonucleotide. NLRP1 directly associates with ASC via its PYD domain, and with caspase-1 via its CARD domain. Human NLRP1 is coded by a single NLRP1 gene, which consists of an amino-terminal PYD, an NOD, LRRs, a function-to-find domain (FIIND), and a carboxy-terminal CARD. In contrast, in mice, there are multiple isoforms of NLRP1 such as Nlrp1a, Nlrp1b, and Nlrp1c, which have the same domain organization but lack a PYD. The NLRP1 inflammasome could spontaneously assemble in cell lysates. Recent studies have identified specific ligands for NLRP1 [20,21]. Muramyl dipeptide (MDP), a peptidoglycan fragment from both gram positive and negative bacteria, can activate NLRP1 in humans, whereas the *Bacillus anthracis* lethal toxin has been indicated to activate mouse NLRP1 [20]. Human NLRP1 was shown to directly bind MDP, causing a structural change in NLRP1 that countenances the binding of ATP, hydrolyzing the NLRP1 oligomerization and recruiting caspase-1 [22]. In addition to caspase-1, NLRP1 also interacts with caspase-5, which presumably contributes to IL-1β processing in human cells (Fabio [10]). The lethal factor, which is associated with alleles of NLRP1, cleaves NLRP1b from LT-responsive and Fisher rats, and induces caspase-1 activation [23]. The mechanisms of NLRP1 activation need to be further elucidated, but K^+ efflux plays an important role in activating NLRP1 [24,25]. It is being reported that variations in the gene encoding NLRP1 are associated with cancer progression, and we will discuss more in the section of 'Pivotal roles of inflammasome in tumor progression'.

2.1.2. NLRP3 inflammasome

NLRP3 (also known as cryopyrin and NAPL3) is the mostly characterized inflammasome and forms an inflammasome complex with ASC and caspase-1. NLRP3 is expressed at low levels in myeloid cells, and is upregulated in response to inflammatory infections and endogenous stimuli,which include PAMPs, DAMPs, ATP, monosodium urate (MSU) [26]. NLRP3 consists of a pyrin domain, an NBD, and an LRR. NLRP3 indirectly recruits procaspase-1 owing to the lack of a CARD domain. NLRP3 interacts with ASC via hemophilic pyrin domain interactions, and then induces the recruitment of procaspase-1 through the CARD domain of ASC. NLRP3 can be activated by the ion flux, reactive oxygen species (ROS), and the lysosomal rupture. Extracellular ATP stimulates the purogenic P2X7 ATP-gate ion channel, and triggers rapid K^+ efflux causing a gradual open of pannexin-1-induced membrane pores [27,28]. Then, ion fluxes enhance the activation of caspase-1 and other inflammasomes [7]. The diverse NLRP3-activating stimuli such as ATP, alum, uric acid, and nigericin. The oxidative stress has been widely involved in NLRP3 activation and the production of ROS. Moreover, the obvious roles of mitochondria and ROS in inflammasome formation and activation have been noted. The NLRP3 inflammasome also senses lysosomal rupture during the "frustrated" phagocytosis of large or crystalline particulate molecules such as MSU, silica, and asbestos. In this process, cathepsin B, a lysosomal cysteine protease, can be produced, which results in the activation of the NLRP3 inflammasome. It was reported that NIMA-related kinase 7 (NEK7) is essential for NLRP3 activation in response to both canonical and non-canonical stimuli acting downstream of the potassium efflux [29,30]. Additionally, polymorphisms of the NLRP3 inflammasome are related to different malignancies such as colon cancer and melanoma [31]. The precise clinical function of NLRP3 in the initiation and promotion of differentiating neoplasms also highlights the therapeutic potential of inflammasomes.

2.1.3. NLRC4 inflammasome

NLRC4 is mainly distributed in hematopoietic tissues and cells and consists of only an N-terminal CARD domain, in addition to a central NBD domain and C-terminal LRRs [32]. NLRC4 directly recruits procaspase-1 via homotypic CARD interactions with other CARD containing proteins and is activated by a diverse variety of bacterial pathogens. For instance, it is believed that NLRC4 senses structural components of the T3SS [33]. To recognize these distinct ligands, NLRC4 in mice interacts the NLR family apoptosis inhibitory proteins (NAIPs) as direct upstream receptors [34]. There are some NAIPs that initiate the NLRC4 inflammasome assembly in mice, whereas humans have only one NAIP, which reportedly responds to the T3SS needle subunit of Chromobacterium violaceum and other bacteria [35,36]. NAIPs then trigger the assembly of the NLRC4 inflammasome complex resulting in the activation of caspase-1 and the release of inflammatory cytokine and pyroptosis [34]. NLRC4 is important for suppressing tumor progression in that tumor suppressor p53 activates the transcription of NLRC4 mRNA and is induced by overexpression of the tyrosine phosphatase, TC-45, which activates p53 [37].

2.1.4. AIM2 inflammasome

AIM2 belongs to the PYHIN family (pyrin and HIN domain family) and is a part of the inflammasome that is stimulated by the detection of cytosolic dsDNA of viral or bacterial origin [38–41], or apoptotic-cell DNA [42,43]. The AIM2 inflammasome can directly bind with cytosolic dsDNA via the HIN-200 domain followed by displacing of the PYD domain and relieving auto-inhibition [44]. The interaction between dsDNA and the HIN domain of AIM2 leads to AIM2 oligomerization around the DNA molecule, which allows for the recruitment of ASC and the activation of caspase-1 [45,46]. According to a recent study, the AIM2 inflammasome protects against *Francisella novidida* infection, which is detected by cGAS and STING by inducing the transcription factor interferon regulatory factor 1 (IRF1) transcription factor. In addition to its role in host defense, AIM2 also plays major role in tumor progression, possibly by sensing self-DNA in the cytosol of cancer cells [47].

2.1.5. PYRIN inflammasome

The pyrin (also known as marenostrin and the tripartite motif (TRIM)-containing 20) inflammasome is encoded by the *MEFV* gene, and it consists of a PYD domain, two B-boxes, and a coiled-coil domain [48]. The pyrin inflammasome is considered as a negative regulator of other inflammasomes or IL-1β activation. Unlike mouse pyrin, human pyrin contains a C-terminal B30.2 domain (also known as a SPRY/PRY) [49,11,50]. The role of the B30.2 domain in human pyrin is inconspicuous, whereas both mouse and human pyrin respond to RHOA modification. It is also reported that pyrin plays a role as a regulator of inflammasome signaling in the process of autophagy cargo binding and

degradation resulting the Familial Mediterranean Fever (FMF)-associated mutations of the B30.2 domain involved in RHOA modification [48].

2.2. Pivotal roles of inflammasomes in cancer progression

2.2.1. Anti-tumorigenic Roles of the Inflammasome

NLR family members are involved in innate immune signaling pathways via the activation or inhibition of the inflammasome. Dysregulation of NLR leads to various inflammatory diseases and autoimmune disorders. NLR acts as a tumor suppressor or tumor promoter in the initiation, progression, and regress of cancer [51].

As we described previously, danger signals such as PAMPs and DAMPs could trigger the formation of the inflammasome complex by assembling with the three components the NLR protein, ASC, and caspase-1, which then leads to the production of inflammatory cytokines such as IL-1β and IL-18 [7]. Overexpression of IL-1β can influence several autoimmune diseases and result in carcinogenesis [52]. Several inflammasomes including NLRP3, NLRP6, NLRC4, NLRP1 and AIM2 have a pathogenic effects in tumor progression as a result of their modulation of innate/adaptive immunity, apoptosis, and differentiation [53]. NLRP3 deficiency is characterized by high susceptibility to colorectal cancer and relevant colon diseases induced by azoxymethane (AOM) and dextran sulfate sodium (DSS) [54,55]. Contrary to these results, a report suggested that NLRP3 is resistant to DSS-induced colitis, but another study insisted that there are no significant differences in the susceptibility to AOM and/or DSS induced colorectal cancer [56]. This might be because various components of the gut microbiota from different animal care facilities can affect the results [57]. According to another study, ASC and caspase-1 deficiencies are liable for colitis-related colorectal cancer, suggesting that ASC and caspase-1 have protective functions in the inflammatory model of colorectal cancer [54,58].

The NLRP3 inflammasome induces the production of IL-18, which potentially represents protective and antitumorigenic functions including the repair of epithelial barrier damages in the case of colitis-associated colorectal cancer [54,55]. Several studies using an IL-18 deficient conditional knockout mouse model have shown inhibitory functions against inflammation and tumor progression [59]. Moreover, the reconstitution of IL-18 in a knockout mouse model could reduce tumor prevalence of tumor via AOM or DSS, implying that inflammasome-producing cytokines such as IL-18 could be potential therapeutic candidates for colorectal cancer [60,55].

NLRP3-mediated IL-18 indirectly inhibits tumor progression in colitis-associated colorectal cancer by skewing the production of IFN-γ from T helper 1 cells and enhancing the cytotoxicity of T cells and NK cells [61,62]. Moreover, NK cells exhibit antitumorigenic effects by inducing the expression of the immunosuppressive molecule PD-1 on their surface [65]. IL-18 positively regulates the biological activity of IL-22, which is critical to protect against intestinal damages in situations of severe inflammation or late stages of tumor progression [63]. However, IL-18 mediates lung metastasis, proving that twice a week administration of recombinant IL-18 via injection exacerbates B16F10 metastasis, whereas it can suppress tumorigenesis when administered daily for five days, and IL-18 deficiency worsens melanoma metastasis [64,65]. This finding suggests that long-term exposure to IL-18 induces antitumorigenic effects, but short-term treatment exerts an opposite effect, indicating that IL-18 blocking antibodies could be used therapeutically to reduce the tumorigenic effects of IL-18.

The NLRP3 inflammasome is important in protecting against cancer progression. The tumor cells that become damaged or die during chemotherapy release ATP, which stimulates the NLRP3 inflammasome and the IL-1β receptor-signaling pathway driving increased activity of cytotoxic T cells against tumor cells. Moreover, chemotherapeutic agent such as oxaliplatin fails to induce the priming of cytotoxic T cells in the NLRP3 deficient mice [66].

The effects of the NLRC4 inflammasome on tumor progression are controvertible because it has dual functions. However, recent studies showed the protective effects against AOM or DSS induced colorectal cancer through the inhibition of STAT3 and antiapoptotic proteins [64]. As a component of NLRC4, the NAIP protein is associated with TLR5 and enhances tumor cell clearance by stimulating the activity of innate immune cells and tumor cell-specific T cell responses [67]. Moreover, NLRC4 stimulates the activation of macrophages and potentiates the production of IFN-γ in T cells suggesting that NLRC4 might attack tumor cells and lead to the increased innate immunity [68].

The AIM2 inflammasome also protects against AOM or DSS-induced colorectal tumorigenesis. AIM2 regulates the phosphorylation of AKT by inhibiting of DNA-dependent protein kinase (DNA-PK) [69]. The inhibition of AKT leads to decreased cell proliferation, which is caused by the prevention of the colonization of a colitogenic microbiota that is less susceptible to colorectal tumorigenesis.

Moreover, accumulated information proved that the polymorphisms or mutation of inflammasome genes is closely associated with the progression of cancer. The polymorphisms of NLRP1 gene were discovered in asbestos-associated mesothelioma patients [3]. The variants of NLRP1/NLRP3 are associated with the susceptibility and clinical features of malignant melanoma [5]. The polymorphisms of NLRP3 inflammasome are considered as high risk factor for the progression of chronic myeloid leukemia (CML) [70]. Additionally, NLRP1 mutations bring increased self-oligomerization and continuous activation of inflammasome, which can cause melanoma and epidermal hyperplasia [6]. NLRP3 is the most critical inflammasome that are involved the progression of cancer.

2.2.2. Tumorigenic roles of the inflammasome

Although there are some studies that show the protective functions of the inflammasomes against cancer, some reports still support the tumorigenic role of inflammasomes [54,56,71]. NLRP3 deficiency results in noticeably diminished lung metastasis, and improved survival of melanoma progression under the dendritic cell therapy. The depletion of NLRP3 caused significantly reduced number of myeloid derived suppressor cells (MDSCs), which suppress the activities of neighboring immune cells [72]. The components of the inflammasome complex can affect tumorigenic effects. One of the main members, ASC, plays dual roles in tumorigenesis, depending on the type of cells and tissues [73]. Using a conditional ASC knockout model in myeloid cells and keratinocytes, it was shown that ASC deficiency in myeloid cells protects against DMBA/TPA-induced skin cancer by inhibiting cell proliferation, implicating the enhanced tumorigenic effect of inflammasomes [74]. ASC also increases cell viability and the proliferation of primary melanoma cells [73].

Furthermore, it is well known that IL-1β and IL-18, which are produced during the activation of the inflammasome pathway, have dual effects in inflammation and tumorigenesis. The proinflammatory cytokine, IL-1β exacerbates melanomas by enhancing tumor growth and invasion, and promotes tumorigenesis by stimulating NF-κB activation and the recruitment of MDSCs [75–77]. IL-1β is significantly involved in the tumorigenesis of several types of cancers, such as gastric cancer and breast cancer. IL-1β signaling induces the activation of MDSCs in the target organ such as the stomach, and exacerbates primary and metastatic mammary tumors, showing its tumorigenic effects [75,77]. The NLRP3 inflammasome can be activated in cancer patients and induces the overproduction of IL-1β in MDSCs during chemotherapy using classical therapeutic agents such as 5-fluorouracil (5-FU) or gemcitabine [78]. IL-1β suppresses the secretion of IL-17 from the CD4 T cells, the cytotoxicity of NK cells, and cytotoxic T cells (CTLs). The NLRC4 inflammasome also produces IL-1β and then accelerates tumorigenesis by mediating vascular endothelial growth factor (VEGF) and vascular angiogenesis [79]. Additionally, IL-1β is related to the unfavorable roles of the NLRP1 inflammasome in epidermal hyperplasia progression [6].

Table 1
The inflammasome inhibitors.

Therapeutic agents	Targets	Effects	Diseases	Status
Anakinra	IL-1 receptor	Recombinant IL-1Ra	RA, Destructive joint process Autoimmune disease (FMF, CAPS, HIDS, TRAPs), Systemic/ common inflammatory diseases (Gout, T2D, Systolic heart failure)	Launched
Rilonacept	IL-1β	Extracellular portion of the IL-1R and the Fc domain of human IgG1	CAPS, Diabetes, Gout	
Canakinumab	IL-1β	Anti-IL-1β antibody	MWS, FCAS	
Ritonavir	Caspase-1	Protease inhibitor	Pancreatitis	
Avastin	P2X7	P2X7 inhibitor	Solid tumor	
Glyburide	NLRP3 (Indirect)	Broad-spectrum inhibitor of the ATP-binding cassette transporter and P2X7R	Type2 diabetes	
N-acetyl Cysteine (NAC)	ROS	ROS generation inhibitor	IBD	
Gevokizumab (Xoma 052)	IL-1β	Anti-IL-1β antibody	Diabetes, Osteoarthritis	Phase II
GSK 1070806	IL-18	Anti-IL-18 antibody	Diabetes, IBD	Phase I/II
Ac-YVAD-CHO	Caspase-1	Caspase-1 inhibitory peptide	Endotoxemia, Pancreatitis	Pre-clinical
VX-765		Selective inhibitor of caspase-1	CAPS, MWS	Pre-clinical
Pralnacasan (VX-740)		Caspase-1 inhibitor	RA	Pre-clinical
Thalidomide		Caspase-1 inhibitor	Myeloma	Phase II
CRID3	ASC	Blocking putative association between GSTO1 and ASC	IBD	Pre-clinical
MCC950		Inhibitor of ASC oligomerization	IBD	Pre-clinical
AZD9056	P2X7	Inhibitor of NLRP3 ATPase	RA	Phase II
224535CE		antagonist	RA, OA	Phase II/III
EVT-401		P2X7 antagonist	RA	Pre-clinical
GSK 1482160		P2X7 antagonist	RA	Pre-clinical
Bay 11-7082	NF-κB /NLRP3 ATPase	Inhibitor of NLRP3 ATPase	Systemic lupus erythematosus	Pre-clinical
Parthenolide	Caspase-1/NF-κB NLRP3 ATPase	Inhibitor of NLRP1/3/4 or caspase-1, inhibitor of NLRP3 ATPase	Dermatitis	Phase II
16673-34-0	NLRP3 (Indirect)	Glyburide derivatives	Acute myocardial infarction	Pre-clinical

2.3. Inflammasomes as therapeutic targets

Excessive activation of the inflammasomes and their substrates shows harmful effects against multiple types of cancer. The complicated and diametric roles of inflammasome components in various cancers suggest that they must be considered as a specific cancer therapy. The development of new therapeutics targeting inflammasomes is still promising, even though inflammasomes have unexpected negative physiological functions. However, targeted inhibition of inflammasome complexes or their signaling pathways could provide a promising opportunity for targeted therapy for human diseases. Moreover, pharmacological inhibitors have limitations, which are relative non-specificity and low efficiency. Promising candidates targeting the inflammasomes or their components have a limitation of off-target effects or unexpected side effects such as the excessive suppression of the inflammasome. To date, more than 50 therapeutic candidates targeting the inflammasomes and their relevant components or signaling pathways are still under development, or have already been launched (Table 1 and Fig. 2) [80,81].

Specific IL-1 receptor inhibitors including those blocking monoclonal antibodies such as anakinra, rilonacept, canakinumab and gevokizumab have been developed and launched for prophylaxis or the treatment of active myeloma by the inhibiting the IL-1β-mediated production of IL-6 [82–84]. IL-1β inhibitors are clinically efficient for treating pulmonary fibrosis but reduce the anti-tumorigenic effect of oxaliplatin or anthracyclines [85]. The clinical use of IL-1β inhibitors should be carefully performed by adjusting the various types of cancer. Anakinra was introduced as a recombinant of IL-1Ra, which can directly block the binding of IL-1R and IL-1 for the treatment of rheumatoid arthritis [86]. Currently, Anakinra is broadly treated to numerous diseases including myeloma cancer (Table 1). Rilonacept is an IL-1 trap that can neutralize circulating IL-1β and IL-1α, preventing direct binding to the IL-1 receptor [82]. Rilonacept originally approved as an orphan drug for the treatment of Cryopyrin-associated periodic syndromes (CAPS). Canakinumab and gevokizumab are humanized monoclonal antibodies of IL-1β that can specifically bind with IL-1β, and block the association with IL-1R, suggesting the prevention against IL-1-induced inflammatory diseases [87].

Avastin (bevacizumab), a specific inhibitor of the P2X7 receptor, which is a trimeric ATP-gated channel that is critical for the NLRP3/caspase-1 cascade, potentiates the inhibition of tumor growth [88]. Avastin was approved to treat various cancers of the breast, colon, and lung by FDA. Avastin efficiently blocks the proliferation of tumor cells and anti-apoptotic genes, the activation of transcription factor NFATc1, and the production of VEGF [89]. Glyburide also known as glybenclamide, inhibits potassium influx and then the maturation of caspase-1 and pro-IL-1β in human monocytes [90,91]. Recent data suggest that glyburide works downstream of the P2X7 receptor but upstream of NLRP3 in human trophoblast [92]. Glyburide was shown to potently block the activation of the NLRP3 inflammasome induced by PAMPs, DAMPs and crystalline substances [92].

Efficient blocking of ASC oligomerization could also be a potential target for developing promising therapeutic treatment for human cancer but these inhibitors are still in the pre-clinical stage. One of the specific inhibitors of ASC components, cytokine release inhibitory drugs (CRIDs), blocks the process of ASC oligomerization in human and murine macrophages in vitro during an early stage of inflammasome activation and regulates disease progression [93]. MCC950, which was discovered as a small-molecule NLRP3 and AIM2 inflammasome inhibitor, potentially inhibits canonical and non-canonical NLRP3 inflammasome activation and IL-1β secretion in mouse model, attenuating the symptoms in severe experimental autoimmune encephalomyelitis (EAE) model and cancer, which indicates it can act as a potent therapeutics against NLRP3 inflammasome-related cancers [94,95]. Currently, parthenolide, BAY-11-7082, and β-hydroxybutyrate are also being developed as specific NLRP3 inflammasome-targeted inhibitors in the mouse models of inflammatory diseases [96,97]. Moreover, microRNAs provide another possibility to inhibit

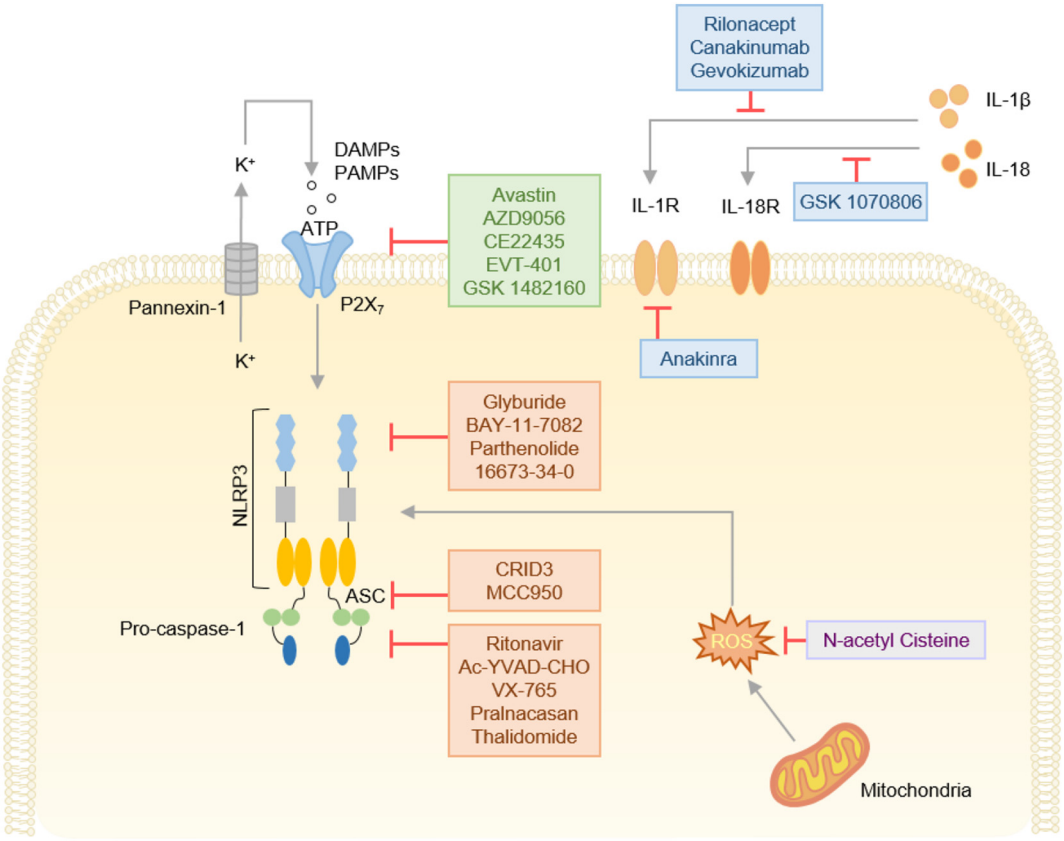

Fig. 2. The status of current inflammasome inhibitors.
Various inhibitors targeting the inflammasome or its relevant components aim to reduce the activities of inflammasomes.

inflammasomes. microRNA-223 inhibits IL-1β production and the expression of NLRP3 by directly binding the 3′ UTR of the NLRP3 transcript and then inhibiting NLRP3 inflammasome activation in murine macrophages or dendritic cells [98]. Some other microRNAs including microRNA-155, microRNA-377, and microRNA-133a-1, are also involved in the activation of the NLRP3 inflammasome [81]. Meanwhile, classical chemotherapeutic agents such as 5-FU also positively regulate NLRP3 inflammasome activation, and even more combined therapy with an IL-β inhibitor results in even more dramatic effects, and decreased side effects and lethal toxicity [78].

Specific caspase-1 inhibitors including ritonavir, disulfiram, and VX-740/765 generally prevent the cleavage of pro-IL-1β into IL-1β [99–101]. Ritonavir was originally developed and launched as a protease inhibitor that was used for the treatment of HIV, and efficiently reduced the level of IL-18 by the blocking caspase-1 in murine pancreatic cancer [100]. VX-765 might be the most commonly developed caspase-1 inhibitor and is a potent and specific caspase-1 inhibitor in animal models in vivo; however, its clinical efficiency is not promising because it is well tolerated and less effective than expected from preclinical data [101]. Thalidomide, which is an immunomodulator, inhibits the activation of the NLRP3 inflammasome related to caspase-1 activation and IL-1β production. Thalidomide directly blocks the caspase-1 activation and IL-1β-IL-6 loop formation in malignant myeloma patients by the blocking of the antiangiogenic activities [102].

Additionally, antioxidants are potent regulator of inflammasome activity due to the inhibition of ROS production, implying the prevention of pro-IL-1β synthesis and NLRP3 expression. *N*-acetyl cysteine (NAC) is a commonly used antioxidant that can block NLRP3 inflammasome activation in human patients [103].Despite the emerging role of inflammasomes in immunity, no drug directly targeting the inflammasomes has been described. The actual limitation of inflammation-related drug discovery for the inflammasome derives from the complexity of the activation pathway, which is not fully understood.

3. Conclusions

In this review, we discussed the overview of the biological importance of inflammasomes in cancer progression and their expected therapeutic effects. As described above, the inflammasome signaling is closely associated with many human cancers. The activation of the inflammasome enhances the secretion of inflammatory cytokines, leading to the infiltration of more immune cells and resulting in the generation and maintenance of an inflammatory microenvironment surrounding cancer cells. In the process of carcinogenesis, the inflammasome also inhibits the anti-carcinogenic activity of NK cell- and T cell-mediated immunosurveillance. Inflammasome also promotes the angiogenesis and metastasis of cancer through the IL-1β-dependent upregulation of chemokines and mediators. The identification of novel tumor-suppressive mechanisms of inflammasome sensors pushes the boundaries of the traditional roles of inflammasomes. Although there are still many knowledge gaps regarding the function of the inflammasomes in carcinogenesis, understanding their signaling pathways, regulatory mechanisms, and pathological significance will enable the development of new therapeutic strategies for the prevention and treatment of human cancers.

Author contributions

I.R. designed and wrote the manuscript. C.L. and H.T.T.D. helped in writing the manuscript and preparing the figures. J.H., D.S. and Y.K. helped in writing and editing manuscript.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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