Inflammasome inhibitors: promising therapeutic approaches against cancer

Shengchao Xu, Xizhe Li, Yuanqi Liu, Yu Xia, Ruimin Chang* and Chunfang Zhang*

Abstract

Inflammation has long been accepted as a key component of carcinogenesis. During inflammation, inflammasomes are potent contributors to the activation of inflammatory cytokines that lead to an inflammatory cascade. Considering the contributing role of inflammasomes in cancer progression, inflammasome inhibitors seem to have a promising future in cancer treatment and prevention. Here, we summarize the structures and signaling pathways of inflammasomes and detail some inflammasome inhibitors used to treat various forms of cancer, which we expect to be used in novel anticancer approaches. However, the practical application of inflammasome inhibitors is limited in regard to specific types of cancer, and the associated clinical trials have not yet been completed. Therefore, additional studies are required to explore more innovative and effective medicines for future clinical treatment of cancer.

Keywords: Inflammasome inhibitors, Therapeutics, Cancer

Background

Inflammasomes are multimeric proteins that promote immune responses and the programmed cell death process known as pyroptosis by the activation of caspase-1 in response to pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). The inflammasome was first described by the team of Dr. Jürg Tschopp in 2002 [1], and this group discovered the features of the inflammasome in cold-associated periodic syndromes, gout and type 2 diabetes in follow-up studies [2]. However, emerging evidence indicates that inflammation triggered by viral or microbial infection plays a crucial role in tumorigenesis [3]. Inflammation associated with cancer progression is triggered by innate immune cells, including dendritic cells, natural killer (NK) cells, and macrophages [4]. Immune cells activated by tumors or tumor components might lead to antitumor immune responses through the recruitment of cytotoxic T cells or the promotion of cancer development by creating a proinflammatory context [5]. A key mechanism inducing inflammation in immune cells is orchestrated by the inflammasome. The activation of the inflammasome leads to the production of interleukin 1β (IL-1β) and interleukin 18 (IL-18) and initiates the programmed cell death process known as pyroptosis [6]. In view of the correlation between the inflammasome and cancer development, inflammasome inhibitors have drawn worldwide attention in the development of novel approaches for cancer treatment.

Inflammasomes consist of NOD (nucleotide oligomerization domain)-like receptors (NLRs), an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and caspase-1. The NLRs generally comprise a leucine-rich repeat (LRR) at the C-terminus, a caspase recruitment domain (CARD) or pyrin domain (PYD) at the N-terminus, and a nucleotide-binding oligomerization domain (NACHT) in the middle. The LRR domain is a sensor that receives signals from PAMPs and DAMPs, while the CARD or PYD interacts with ASC [1]. Immune cells activated by tumors or tumor components might lead to antitumor immune responses through the recruitment of cytotoxic T cells or the promotion of cancer development by creating a proinflammatory context [5]. A key mechanism inducing inflammation in immune cells is orchestrated by the inflammasome. The activation of the inflammasome leads to the production of
C-terminal HIN domain and an N-terminal PYD, through which AIM2 can recruit ASC and caspase-1 to form the AIM2 inflammasome [10].

As a key regulator in inflammation, inflammasomes can activate inflammatory cytokines such as IL-1β and IL-18 in response to PAMPs or DAMPs [11]. The NLRP1 inflammasome is activated by muramyl dipeptide, Bacillus anthracis lethal toxin, and Toxoplasma gondii, and the NLRP3 inflammasome can be activated by the combination of mtDNA and cardiolipin. Recognition of NAIP family members induces the activation of the NLRC4 inflammasome, whereas the AIM2 inflammasome can be activated by direct binding with dsDNA via its HIN domain [12]. Inflammasome activation induces the production of IL-1β, which has been implicated in metabolic disorders. Studies have shown that IL-1β plays critical roles in type 2 diabetes and gout and that the blockade of IL-1β exhibits high efficacy in clinical trials [13, 14]. Moreover, the inflammasome is increasingly suspected of playing critical roles in autoinflammatory disorders, Alzheimer’s disease, and cancer [15].

In this review, we summarize the structures and functions of inflammasomes and the signaling pathway that activates inflammasomes, which induce inflammatory cascades. In this regard, multiple drugs that inhibit inflammasomes have been generalized as novel medications against various types of cancer, and some are worthy of further study. Finally, we list some inflammasome inhibitors whose anti-inflammatory activities are well proven. However, their antitumor activities remain to be discovered. Considering the correlation between inflammation and cancer development, these drugs are expected to be innovative therapeutics for cancer treatment.

**Inflammasome signaling pathway**

Canonical inflammasome activation requires two signals. The first signal, defined as priming, is the recognition of a DAMP or PAMP by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NLRs, which initiate innate and adaptive immunity. Here, we focus on the role of NLRs due to their necessity in forming the inflammasome complex. In response to the recognition of a PAMP or DAMP, NLRs oligomerize into homo- or heteroproteins and activate NF-κB. The activation of NF-κB induces the mRNA and protein expression...
of pro-IL-1β and pro-IL-18 [16]. The second signal is triggered by diverse stimuli activating NLRs, leading to the assembly of inflammasomes via the CARD domain in ASC, which can recruit caspase-1 and interact with NLRPs [17]. When caspase-1 is associated with NLRPs and ASC, the inflammasome complex promotes autocatalytic cleavage of caspase-1, forming the active form of the caspase-1 enzyme [18]. Active caspase-1 can activate pro-IL-1β and pro-IL-18, which are inflammatory cytokines that generate inflammation responses [19]. Moreover, active caspase-1 also leads to the programmed cell death process termed pyroptosis in certain circumstances. In contrast to apoptosis, pyroptosis results in the rupture of the plasma membrane and release of DAMP molecules such as ATP and IL-1α into the extracellular space, which recruits more immune cells and further promotes the inflammatory cascade [20].

In contrast to the canonical pathway, the noncanonical pathway engages caspase-11 or caspase-8. In response to pathogens such as Escherichia coli, Citrobacter rodentium, or Vibrio cholera, caspase-11 is activated, leading to caspase-1-independent macrophage cell death and caspase-1-dependent IL-1β and IL-18 secretion [21]. In addition, the combination of fungi, Mycobacteria, and the dectin-1 receptor can trigger the formation of the noncanonical inflammasome complex consisting of MALT1, caspase-8, and ASC, which induces the activation of pro-IL-1β and the maturation of IL-1β [22].

Both the priming and the activation of the inflammasome are regulated by a deubiquitination mechanism. The application of G5, an inhibitor of deubiquitination, suggests the involvement of a deubiquitinating enzyme in the activation of the NLRP3 inflammasome. BRCC3, a deubiquitinating enzyme, was identified to regulate NLRP3 ubiquitination by targeting the LRR domain [23]. Moreover, IL-1R-associated kinase (IRAK) plays a critical role in NLRP3 priming by regulating NLRP3 deubiquitination, as demonstrated by using deficient mouse models. IRAK1 and IRAK4 interact with MyD88 in the transcriptional priming phase, whereas IRAK1 regulates posttranslational NLRP3 activation via the TRIF pathway [24]. Notably, the involvement of mitochondrial reactive oxygen species (mtROS) continues to be debated [25]. The deubiquitination pathway mediated by MyD88 is demonstrated to be mtROS dependent and can be inhibited by antioxidants; however, signaling by ATP can also induce the deubiquitination of NLRP in an mtROS-independent manner [26].

There also exist two molecules—heat shock protein 90 (HSP90) and the ubiquitin ligase-associated protein SGT1—that are important for NLRP3 activation. Downregulation of SGT1 expression by siRNA or chemical inhibition of HSP90 can significantly decrease inflammasome activity, leading to repression of NLRP3-mediated gout-like inflammation in mice. Moreover, the interaction of these molecules with NLRP3 is suggested to maintain NLRP3 in an inactive state. Once activating signals are detected, HSP90 and SGT1 dissociate from NLRP3, allowing inflammasome oligomerization [27].

Mitochondrial dysfunction is also involved in inflammasome activation. After the recognition of activating signals such as ATP or LPS, mitochondrial DNA is released into the cytosol and then bound directly by the NLRP3 inflammasome, leading to the activation of the inflammasome and maturation of caspase-1 [28]. During the binding of mtDNA and NLRP3, mitochondrial antiviral signaling protein (MAVS) and mitofusin2 (Mfn2) are thought to be implicated in NLRP3 activation; however, the actual interactions and functions of these proteins are not yet known [29, 30].

Thus, inflammasomes are essential in the immune system, and their roles in the activation of inflammation are incontrovertible. During inflammation, the stimulated inflammasome rapidly produces activated caspase-1, leading to cell pyroptosis and the release of inflammatory cytokines. Inflammatory cytokines are believed to participate in the processes of angiogenesis, metastasis, and epithelial-to-mesenchymal transition activation, which substantially contributes to cancer development [31]. Concerning the relationship between inflammation and cancer, the inflammasome appears to play a detrimental role in cancer due to its proinflammatory activity. However, the direct effect of inflammasome activation on cancer promotion remains controversial.

Contrasting roles of inflammasomes in cancer

Previous studies have shown that the activated inflammasome plays contrasting roles in cancer promotion and therapy [32]. A protective role for the inflammasome has mainly been observed in colitis-associated cancer. Dextran sulfate sodium (DSS) and azoxymethane (AOM) plus DSS mouse models show increases in the incidences of acute and recurrent colitis-associated cancer in mice lacking inflammasome genes, which are correlated with the levels of IL-1β and IL-18 at the tumor site [33–36]. Moreover, bone marrow reconstitution experiments have demonstrated increased inflammation and tumorigenesis in colitis-associated colon cancer in mice lacking NLRP1 [37]. Additionally, caspase-1-deficient mice have enhanced tumorigenesis as a result of increasing colonic epithelial cell proliferation in the early stage of cancer and reducing apoptosis in advanced colon cancer [38]. In other malignancies, NLRC4 suppresses the tumor growth of melanoma by stimulating tumor-associated macrophages and generating protective T cells [39]. In addition, elevating AIM2 expression by delivering an exogenous AIM2 promoter can significantly inhibit the proliferation and invasion of renal carcinoma [40]. Furthermore, the activation
of NLRP1 by serine dipeptidases 8 (DPP8) and DPP9 mediates caspase-1-dependent pyroptosis in human acute myeloid leukemia [41]. This antitumor activity achieved by inhibiting NLRP1 is also exhibited in chronic myeloid leukemia [42].

However, the activation of the inflammasome can also facilitate tumor development. In a mouse model of intravenous injection of B16-F10 melanoma cells, researchers found that mice lacking NLRP3 had a significant decrease in lung metastases compared with wild-type mice and that the pathway was independent of caspase-1 and IL-1β [43]. An analysis of tissue-specific knockout mouse strains fully deficient in ASC used in a chemical-induced skin carcinogenesis model showed that ASC affected tumor proliferation in a dichotomous way: it favored tumor growth via a proinflammatory role in infiltrating cells, while it also limited keratinocyte proliferation and thus helped to suppress tumors [44]. However, ASC protein expression is repressed in metastatic melanoma compared with primary melanoma, and inflammasome-associated caspase-1 and IL-1β are inhibited when the ASC gene is inhibited in primary and metastatic melanoma cells [45]. Moreover, researchers have found that in animal and human breast cancer models, the inflammasome and IL-1β pathway promotes tumor proliferation and migration and that mice lacking inflammasome components exhibit notably suppressed tumor growth and lung metastasis [46]. Additionally, among risk factors for breast cancer, obesity has been associated with a poor clinical prognosis. Studies have found that the activation of the obesity-associated NLRC4 inflammasome drives breast cancer progression [47]. However, in pancreatic ductal adenocarcinoma, studies have demonstrated that the inhibition or deletion of NLRP3, ASC, or caspase-1 decreases tumor growth and metastasis by reprogramming innate and adaptive immunity in the tumor microenvironment [48]. A detrimental role for NLRP3 has also been observed in malignant mesothelioma [49]. AIM2, a subtype of inflammasome, was reported to be a cancer suppressor gene in early years. A recent study showed that AIM2 was highly expressed in non-small cell lung cancer (NSCLC) and promoted tumor development in an inflammasome-dependent manner [50]. As a molecule downstream of the inflammasome, IL-1β has been demonstrated to promote tumor progression by recruiting myeloid-derived suppressor cells, which might inhibit the antitumor immune response [51].

Considering the aforementioned findings, the inflammasome seems to play contrasting roles in cancer development. We hypothesize that different immune responses determine the role of the inflammasome in different types of cancer. In most malignancies, the activation of the inflammasome can lead to either immune surveillance against the tumor or an inflammatory response that promotes cancer development. In colon cancer, the activation of the inflammasome protects the epithelium from cancer invasion. A recent study found that mice deficient in IL-18 and IL-18 receptor but not wild-type mice are highly susceptible to AOM/DSS-induced colon cancer [52]. Considering that DSS induces mucosal damage in the intestinal epithelium, IL-18 secreted during inflammasome activation might be able to maintain the homeostasis of the epithelial barrier, which could account for its antitumor activity. On the other hand, this study showed that epithelial-derived IL-18 could directly interact with CD4+ T cells, leading to the suppression of Th17 cell differentiation. However, IL-18 receptor is critical in Foxp3+ Treg cells, which mediate the reduction in intestinal inflammation [53]. These findings suggest that the activation of the inflammasome induces the production of IL-18 and that IL-18 then reduces intestinal inflammation by repressing Th17 cells and elevating Treg function. The reduction in inflammation maintains the homeostasis of the intestinal epithelium, leading to the suppression of colon cancer. Further investigations are warranted to verify this hypothesis. The heterogeneity of the inflammasomes in various cancers suggests that inhibitor application should be tailored to the specific situation.

**Antitumor effects of inflammasome inhibitors**

As excessive inflammation induced by the inflammasome can be a detrimental factor in multiple types of cancer, inflammasome inhibitors appear to be a promising approach for cancer prevention and treatment. Currently, many drugs and molecules have been shown to regulate inflammasome activity. However, some of them target the noncanonical signaling pathway of the inflammasome or indirectly affect the functions of the inflammasome by targeting other molecules. Here, we have listed the drugs targeting the canonical signaling pathway of the inflammasome and the antagonists most investigated in cancer treatment (Fig. 2; Table 1).

**Drugs already used in clinical applications**

**Thalidomide**

In the past, thalidomide has mainly been used as a sedative or hypnotic drug to treat anxiety, insomnia, gastritis, and tension [79]. The antitumor activity of thalidomide was discovered when it was used for the treatment of erythema nodosum leprosum because of its antiangiogenic properties [80]. However, due to its potential to cause congenital defects, thalidomide analogs have mostly been applied to many types of cancer, including prostate cancer and multiple myeloma.

For the treatment of multiple myeloma, thalidomide has been approved for first-line therapy in combination with other chemotherapeutic drugs [81]. In patients with
relapsed myeloma, few therapies are available. However, researchers have found that thalidomide has a practical antitumor effect on patients with advanced myeloma. According to statistics, 10% of patients experience complete or almost complete remission and 32% exhibit a decrease in serum or urine paraprotein levels. In most patients, the percentage of plasma cells in the bone marrow is reduced, and the hemoglobin level is elevated, indicating substantial antitumor activity against myeloma [55]. In a randomized phase II trial, the combination of thalidomide and docetaxel resulted in a significant reduction in the prostate-specific antigen level and an elevation of the median survival rate in patients with metastatic androgen-independent prostate cancer [54]. The mechanism of malignancy control with thalidomide might involve its antiangiogenic activity. Thalidomide was demonstrated to reduce the high levels of certain angiogenic factors, such as fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) [82]. Moreover, thalidomide enhances cell-mediated immunity by directly interacting with cytotoxic T cells, which are lethal to tumor cells [83].

However, the application of thalidomide in other carcinomas has not shown significant efficacy. In unresectable hepatocellular carcinoma, thalidomide is tolerated in most patients with gradual dose escalation, but its monotherapeutic activity is modest compared with that of the combined therapy [84]. In a randomized, double-blinded, placebo-controlled trial, 722 patients with advanced non-small cell lung cancer were treated with thalidomide in combination with gemcitabine and carboplatin. The results showed that this treatment regimen did not improve the survival rate but did increase the risk of thrombotic events [85]. Moreover, this outcome was also demonstrated in a phase III clinical trial performed in France, and neuropathy was the most common adverse event observed [86]. Additionally, in patients with metastatic melanoma, the combination of thalidomide and dacarbazine or temozolomide shows limited efficacy. Constipation, peripheral neuropathy, fatigue, edema, and rash are attributed to thalidomide [87, 88].

Overall, thalidomide is widely used in the treatment of multiple myeloma and prostate cancer. Especially in multiple myeloma, the combination of melphalan-prednisone-thalidomide is deemed a standard therapy for patients ineligible for stem cell transplantation [89]. However, its antitumor activity has a moderate effect on other types of cancer.

---

**Fig. 2** Signaling pathway and inhibitors of inflammasomes. The priming of the inflammasome is initiated by the recognition of a PAMP or DAMP, which mediates the activation of NF-kB. The activation of NF-kB induces the production of NLRP3 and the generation of pro-IL-1β and pro-IL-18. After deubiquitination and combination with mtDNA, NLRP3 interacts with ASC and caspase-1, forming the inflammasome complex. The inflammasome is activated by the recognition of P2X7R, leading to the cleavage of caspase-1. Active caspase-1 then promotes the secretion of IL-1β and IL-18, which is the key to inducing inflammasome-dependent inflammation. Inflammasome inhibitors target the upstream and downstream molecules in the inflammasome signaling pathway. Arrows denote an activating effect, and blunted lines denote targets inhibited by selective compounds.
Anakinra

Anakinra is a recombinant form of interleukin-1 receptor antagonist (IL-1Ra), which is commonly applied in the treatment of rheumatoid arthritis and autoimmune disease [90].

Previous studies with myeloma cells have shown that anakinra can significantly reduce IL-6 levels but does not increase myeloma cell death. However, a combination therapy of anakinra and dexamethasone induces cell death in myeloma cells [91]. In a study of breast cancer mouse models, anakinra decreased the growth of tumors in the bone and reduced the number of mice with bone metastasis from 90% (placebo) to 40% (treatment) or 10% (preventative). This study indicated that anakinra fails to increase tumor cell death but represses cell proliferation and angiogenesis [57]. Melanoma, the most dangerous type of skin cancer, has a poor prognosis. A study found that anakinra increases M1 macrophage polarization and decreases myeloid-derived suppressor cell numbers in mice with melanoma [56]. In phase II clinical trials, researchers investigated the roles of anakinra and low-dose dexamethasone in patients with smoldering or indolent multiple myeloma. The results showed that anakinra targets the progressed myeloma fraction in vivo and decreases the proliferation of myeloma cells [58]. Then, the antitumor activity of anakinra was mainly mediated by reducing angiogenesis. The administration of anakinra alleviated the levels of CD34-positive blood vessels and significantly reduced the expression of the endothelin 1 gene [57]. Moreover, previous studies have shown that IL-1β elevates the expression of VEGF and VEGF represses the activities of IL-1β [92, 93]. The inhibition of IL-1β by anakinra could obviously suppress the activity of VEGF, leading to an antiangiogenic effect.

Anakinra is usually used as a second-line treatment in rheumatoid arthritis, and subcutaneous injection of anakinra has been approved by the US FDA [94]. However, the antitumor applications of anakinra await further studies.

### Drugs studied in clinical trials

#### P2X7R antagonist

Previous studies have demonstrated that P2X7 is highly expressed in prostate cancer, pancreatic ductal adenocarcinoma (PDAC), head and neck squamous cell carcinoma, colorectal cancer, and papilloma. When the expression of P2X7 is downregulated by siRNA, the metastasis and invasion of prostate cancer cells are notably reduced through the PI3K/AKT and ERK1/2 pathways [59]. In PDAC, P2X7R allosteric inhibitor-treated cells exhibited attenuated tumor proliferation and invasion compared to untreated control cells [60]. Extracellular ATP and BzATP, which have relatively high affinities for P2X7R, further impact cell survival and the complex function of P2X7R [61]. Moreover, P2X7R plays an important role in bone tumor growth and functions [95]. In osteosarcoma, P2X7R was proven to facilitate the growth and matrix invasion of tumor cells, which indicates the potential of P2X7R as a therapeutic target [62]. In another bone cancer, multiple myeloma, the activation of P2X7R was also deemed to affect cell necrosis in the RPMI-8226 cell line [63]. Furthermore, the inhibition of P2X7R can lead to decreased invasiveness in A253 cells, which are derived from an epidermoid carcinoma [64]. Since chronic inflammation is a key factor leading to colorectal cancer, P2X7R has been documented as a regulator in inflammatory responses. In

| Drug                  | Target          | Effective cancer type                                      | Clinical trials | Reference |
|-----------------------|-----------------|-----------------------------------------------------------|----------------|----------|
| Thalidomide           | Caspase-1       | Prostate cancer                                           | Phase II       | [54]     |
|                       |                 | Multiple myeloma                                         | Phase III      | [55]     |
| Anakinra              | IL-1R           | Melanoma                                                 | N/A            | [56]     |
|                       |                 | Breast cancer                                            |                | [57]     |
|                       |                 | Multiple myeloma                                         | Phase II       | [58]     |
| P2X7R antagonist      | P2X7R           | Prostate cancer                                           | N/A            | [59]     |
|                       |                 | Pancreatic ductal adenocarcinoma (PDAC)                   | [60, 61]       |          |
|                       |                 | Osteosarcoma                                             | [62]           |          |
|                       |                 | Multiple myeloma                                         | [63]           |          |
|                       |                 | Head and neck squamous cell carcinoma                    | [64]           |          |
|                       |                 | Colorectal cancer                                        | [65]           |          |
|                       |                 | Basal cell carcinoma                                     | Phase I        | [66]     |
| Parthenolide          | NF-κB           | Gastric cancer                                           | N/A            | [67]     |
|                       |                 | Colorectal cancer                                        |                | [68]     |
|                       |                 | Pancreatic adenocarcinoma                                |                | [69]     |
|                       |                 | Nasopharyngeal carcinoma                                 |                | [70]     |
| Andrographolide       | NF-κB           | Insulinoma                                               | N/A            | [71]     |
|                       |                 | Colorectal cancer                                        | [72–74]        |          |
|                       |                 | Breast cancer                                            | [75, 76]       |          |
|                       |                 | Multiple myeloma                                         | [77]           |          |
| Canakinumab           | IL-1β           | Lung cancer                                              | Phase III      | [78]     |
|                       |                 | (undergoing)                                             |                |          |

### Table 1: Studies and clinical trials of inflammasome inhibitors in cancer

| Drug                  | Target          | Effective cancer type                                      | Clinical trials | Reference |
|-----------------------|-----------------|-----------------------------------------------------------|----------------|----------|
| Thalidomide           | Caspase-1       | Prostate cancer                                           | Phase II       | [54]     |
|                       |                 | Multiple myeloma                                         | Phase III      | [55]     |
| Anakinra              | IL-1R           | Melanoma                                                 | N/A            | [56]     |
|                       |                 | Breast cancer                                            |                | [57]     |
|                       |                 | Multiple myeloma                                         | Phase II       | [58]     |
| P2X7R antagonist      | P2X7R           | Prostate cancer                                           | N/A            | [59]     |
|                       |                 | Pancreatic ductal adenocarcinoma (PDAC)                   | [60, 61]       |          |
|                       |                 | Osteosarcoma                                             | [62]           |          |
|                       |                 | Multiple myeloma                                         | [63]           |          |
|                       |                 | Head and neck squamous cell carcinoma                    | [64]           |          |
|                       |                 | Colorectal cancer                                        | [65]           |          |
|                       |                 | Basal cell carcinoma                                     | Phase I        | [66]     |
| Parthenolide          | NF-κB           | Gastric cancer                                           | N/A            | [67]     |
|                       |                 | Colorectal cancer                                        |                | [68]     |
|                       |                 | Pancreatic adenocarcinoma                                |                | [69]     |
|                       |                 | Nasopharyngeal carcinoma                                 |                | [70]     |
| Andrographolide       | NF-κB           | Insulinoma                                               | N/A            | [71]     |
|                       |                 | Colorectal cancer                                        | [72–74]        |          |
|                       |                 | Breast cancer                                            | [75, 76]       |          |
|                       |                 | Multiple myeloma                                         | [77]           |          |
| Canakinumab           | IL-1β           | Lung cancer                                              | Phase III      | [78]     |
|                       |                 | (undergoing)                                             |                |          |

Xu et al. Journal of Hematology & Oncology (2019) 12:64 Page 6 of 13
colorectal cancer patients, high expression of P2X7R is significantly associated with tumor size and lymph node metastasis [65]. High expression of P2X7 enhances cancer proliferation, migration, invasion, and angiogenesis. Cancer cells can downregulate the expression of P2X7 to avoid apoptosis and use ATP as an invasion-promoting signal [96]. The activation of P2X7 promotes cancer invasion by releasing cathepsin and MMP-9 [97, 98]. Moreover, the P2X7-dependent release of VEGF promotes angiogenesis and contributes to cancer development [99]. These findings suggest that P2X7R antagonists alter the context of tumor cells, leading to the suppression of cancer progression.

In clinical trials, the safety and tolerability of a P2X7 antagonist were assessed in an open-label, phase I study, in which approximately 65% of patients with basal cell carcinoma showed a decrease in lesion area and the most common adverse event was an allergic reaction occurring at the treatment site [66]. These properties warrant additional studies to evaluate the potential of P2X7 antagonists in the treatment of not only skin cancer but also other malignancies.

Parthenolide
Parthenolide is a sesquiterpene lactone compound found in the herb named feverfew, which is used as an anti-inflammatory medicine [100]. While NF-κB has been reported to be a key factor regulating a number of genes that are crucial for tumor invasion and metastasis, parthenolide is considered a potential antitumor therapeutic drug that functions by inhibiting the NF-κB signaling pathway [101]. In gastric cancer, parthenolide significantly inhibits tumor cell growth and downregulates the phosphorylation of NF-κB. During a study of combined therapy with parthenolide and paclitaxel, the survival time of patients with gastric cancer was notably prolonged [67]. In addition, in pancreatic adenocarcinoma, tumor cell growth can be inhibited by parthenolide in a dose-dependent manner. After a higher concentration of parthenolide treatment is administered, internucleosomal DNA fragmentation indicative of apoptosis can be observed [69]. In a study of colorectal cancer models, intraperitoneal injection of parthenolide notably inhibited tumor proliferation and angiogenesis. By focusing on the Bcl-2 family in cancer cells, a parthenolide-mediated cell death signaling pathway was investigated and confirmed to be associated with colorectal cancer cell death [68]. In nasopharyngeal carcinoma, parthenolide induces tumor cell death through the NF-κB/COX-2 pathway. Using COX-2 inhibitors or knocking down COX-2 expression with siRNA or shRNA suppresses cancer stem-like cell phenotypes. Parthenolide exerts an inhibitory effect on NF-κB by suppressing both the phosphorylation of IkB kinase and the degradation of IkBα [70]. The mechanisms involved in the antitumor activity of parthenolide, including the inhibition of NF-κB, activation of JNK, activation of p53, and suppression of STAT3, have attracted great interest. Parthenolide sensitizes cancer cells to TNF-α-induced apoptosis by inhibiting NF-κB and activating JNK [102]. The administration of parthenolide can activate p53, leading to a reduction in cancer cell proliferation [103]. Moreover, parthenolide can inhibit the activation of STAT proteins by blocking their tyrosine phosphorylation, which is indispensable for STAT translocation into the nucleus and target gene activation [104].

In practical use, the low solubility and bioavailability of parthenolide limit its potential [105]. However, creating synthetic analogs of parthenolide may be a novel way to address this problem [106]. Currently, a clinical trial of parthenolide is being performed in allergic contact dermatitis [107]. Therefore, additional studies are required to exploit parthenolide as a novel antitumor drug.

Canakinumab
Canakinumab is a human monoclonal antibody targeting IL-1β but not IL-1α. In 2009, canakinumab was authorized by the US Food and Drug Administration and European Medicines Agency as a treatment for cryopyrin-associated periodic syndromes [108]. A randomized, double-blinded trial found that compared with controls, canakinumab at a dosage of 150 mg every 3 months led to a notable reduction in the rate of recurrent cardiovascular events [109]. When cancer is considered, canakinumab still deserves recognition. During a randomized, double-blinded, placebo-controlled trial of patients with lung cancers and atherosclerosis, researchers found that canakinumab could significantly decrease lung cancer mortality by targeting the IL-1β innate immunity pathway. It is worth mentioning that this antitumor effect is mostly detected in patients with lung adenocarcinoma or poorly differentiated large cell cancer, whereas meaningful assessments of the effects on patients with small cell lung cancers or squamous cell carcinomas have rarely been performed [78]. The chronic use of aspirin can reduce mortality in colorectal cancer and lung adenocarcinomas due to its anti-inflammatory activity [110, 111], and canakinumab is theorized to combat cancer in a similar way, according to its function of inhibiting the inflammasome [78].

Currently, the application of canakinumab as an antitumor drug is mainly focused on lung cancer. Canakinumab is being studied in phase III clinical trials in non-small cell lung cancer to evaluate its tolerability and efficacy compared with those of a placebo. Consequently, the completion of the clinical trials is warranted to determine whether canakinumab can be used safely and effectively in cancer treatment.
**Andrographolide**
Andrographolide is a labdane diterpenoid that has been isolated from the stem and leaves of *Andrographis paniculata* [112]. Numerous studies have validated the facts that andrographolide can inhibit cell invasion and induce cell death in various types of cancer cells. A recent study showed that andrographolide significantly reduces tumor cell proliferation at both the early stage and advanced stage of insulinoma by targeting the TLR4/NF-κB signaling pathway [71]. In addition, in colon cancer, andrographolide represses cell proliferation, elevates cell apoptosis, and activates caspase-3/9 in SW620 human colon cancer cells by inhibiting NF-κB, TLR4, MyD88, and MMP-9 signaling activation [72]. Among chemotherapeutic drugs, 5-fluorouracil (5-Fu) is the one most commonly used in colorectal cancer. Andrographolide can promote the 5-Fu-induced antitumor effect by repressing the level of phosphorylated cellular-mesenchymal to epithelial transition factor [73]. In colitis-associated cancer, andrographolide inhibits the NLRP3 inflammasome, protecting mice against dextran sulfate sodium-induced colon carcinogenesis [74]. In breast cancer, andrographolide suppresses breast cancer-induced osteolysis by inhibiting the NF-κB and ERK signaling pathway at a relatively low dose and by promoting apoptosis at a relatively high dose. Its antitumor activity correlates with the downregulation of the NF-κB signaling pathway [75, 76]. Moreover, andrographolide reduces proliferation and increases cell apoptosis by downregulating the protein expression of TLR4 and NF-κB in multiple myeloma [77]. The antitumor mechanisms of andrographolide include the inhibition of the NF-κB pathway [113], suppression of cyclins and cyclin-dependent kinases [114], and activation of the p53 protein [114], leading to reductions in cancer cell proliferation, invasion, and angiogenesis.

Clinical trials of andrographolide have mainly focused on inflammatory diseases such as acute upper respiratory tract infections [115, 116], and its antitumor activity has been demonstrated only in vitro. Therefore, more studies are required to investigate its application in cancer treatment.

Overall, clinical application was limited to only anakinra and thalidomide, and other drugs are still under assessment in clinical trials. All of these drugs inhibit the production and activation of inflammasome-associated molecules such as P2X7R, IL-1, NF-κB, and caspase-1, leading to the suppression of the inflammasome. As mentioned above, the antitumor mechanisms of these drugs involve the regulation of the expression of p53, NF-κB, STAT, and VEGF, leading to the suppression of tumor cell proliferation, metastasis, invasion, and angiogenesis. However, the direct interactions of inflammasome inhibitors involved in repressing cancer development are not yet known. Further studies are needed to explore the mechanisms in a more explicit way.

**Potential antitumor drugs**
Considering the correlation between inflammation and tumorigenesis, it is rational to expect that antagonists that inhibit the initiation of inflammation could be explored as potential antitumor drugs. In the inflammasome signaling pathway, there are many steps that could be targeted, such as the assembly and activation of inflammasomes, the synthesis of IL-1, and the generation of caspase-1. Several inhibitors targeting the above processes hold promise in developing novel drugs against cancer and are described below.

**Glyburide**
Glyburide is an antidiabetic drug in a class of medications known as sulfonylureas, which are commonly used in the therapy of type 2 diabetes [117]. Glyburide was demonstrated to block ATP-sensitive potassium channels in pancreatic β cells [118]. In placental inflammation-associated diseases, trophoblasts can secrete IL-1β through the NLRP3 pathway, which plays an important role in inflammation-associated pregnancy complications, and glyburide offers considerable therapeutic promise as an inhibitor of the NLRP3 inflammasome [119]. Moreover, glyburide was beneficial in human melioidosis in a study of 1160 patients with gram-negative sepsis due to its inhibitory effect on the inflammasome and subsequent suppression of the inflammatory response. Considering the role of the NLRP3 inflammasome in endotoxemia, the data suggest that glyburide can delay lipopolysaccharide (LPS)-induced lethality in mice [120]. However, since glyburide specifically inhibits the NLRP3 inflammasome in vitro, treatment requires the administration of a high dose in vivo, which causes hypoglycemia and is beyond its pharmacological action in type 2 diabetes. A recent finding suggests that the small molecule 16673-34-0, which is an intermediate substrate in the synthesis of glyburide, disrupts the synthesis of the NLRP3 inflammasome and limits infarct size in mouse models of myocardial infarction without affecting glucose metabolism [121]. Therefore, this substrate, which exhibits pharmacodynamics similar to those of glyburide, may be a novel inhibitor of the inflammasome with fewer side effects than glyburide.

**CRID3/MCC950**
The cytokine release inhibitory drugs (CRID3), also known as MCC950, are diaryl sulfonylurea-containing compounds that inhibit the activation of the NLRP3 inflammasome both in mice in vivo and in human cells in vitro [122]. Researchers have found that CRID3 inhibits the secretion of IL-1β and caspase-1 in response to the NLRP3 and AIM2 inflammasomes but not in response to the NLRC4 inflammasome. In contrast to the NLRP3 inhibitors glyburide and parthenolide, CRID3...
can prevent AIM2-dependent pyroptosis. Moreover, the potential target of CRID3 was identified as glutathione S-transferase omega 1 (GSTO1), a protein that has been demonstrated to interact with ASC [123, 124]. In a study of a spontaneous chronic colitis mouse model, MCC950 resulted in significant suppression of IL-1β secretion and activation of caspase-1, indicating a potential novel avenue for treatment of human colonic inflammation diseases [125].

**Pralnacasan**

Pralnacasan is an orally absorbed nonpeptide compound that inhibits interleukin 1β converting enzyme (ICE), which is also known as caspase-1 [126]. ICE exists in the plasma membrane of monocytic cells where it activates the precursors of IL-1β and IL-18 into their active forms. This process is considered to be downstream in the inflammasome signaling pathway [127, 128]. In a collagenase-induced osteoarthritis mouse model, pralnacasan has been demonstrated to reduce joint damage, indicating its potential as a disease-modifying drug for the therapy of osteoarthritis [129]. In dextran sulfate sodium (DSS)-induced murine colitis models, pralnacasan is able to ameliorate dextran sulfate sodium-induced colitis with almost no side effects. This process is probably mediated by the repression of the inflammatory cytokines IL-1β and IL-18 [130]. Researchers found that IL-18 mRNA and TNF-α mRNA levels were elevated in DSS-induced colitis, and the administration of pralnacasan significantly reduced the expression of IL-18 mRNA but did not affect the expression of TNF-α mRNA. Therefore, the therapeutic approach of combining TNF-α expression-reducing substances with pralnacasan appears to be a promising idea [131].

**VX-765**

VX-765, also known as belnacasan, is an inhibitor that decreases the activity of caspase-1. A study showed that the administration of VX-765 in rat models significantly reduced the number of seizures and delayed the time to seizure onset [132]. The same anticonvulsant effect of VX-765 has been exhibited in mice models in a dose-dependent manner [133]. Moreover, the application of VX-765 stops the accumulating deposition of amyloid β, indicating its potent therapeutic activity in Alzheimer’s disease [134]. In addition to its inhibitory effect on nervous system disease, VX-765 has also been proven to reduce infarct size in a rat model of myocardial infarction. In combination with an antiplatelet P2Y12 inhibitor, VX-765 exhibited a highly protective function when myocardial infarction occurred [135, 136].

Currently, clinical trials of VX-765 are mainly studying the treatment of epilepsy. A randomized, double-blinded, placebo-controlled phase II study of VX-765 in patients with treatment-resistant partial epilepsy was completed, and the results showed no statistically significant difference between the VX-765 group and the placebo group [137]. Consequently, a longer duration study is warranted to measure the clinical efficacy of VX-765.

**Ac-YVAD-CHO**

Ac-YVAD-CHO is a polypeptide with a sequence homologous to the known sequences of caspase substrates, which accounts for its ability to inhibit the activation of caspase-1 [138, 139]. Researchers have used Ac-YVAD-CHO as a therapeutic intervention in pancreatic carcinoma cells, and they found that the inhibition of caspase-1 leads to cell apoptosis. Moreover, according to their observations, caspase-1 was directly involved in anti-apoptotic processes in pancreatic cancer [140]. Additionally, the administration of Ac-YVAD-CHO has been demonstrated to induce remission in rats with endotoxemia by decreasing the secretion of IL-1β and IL-18 [141].

Overall, caspase-1 and IL-1β, molecules downstream of the inflammasome, play major roles in the generation of inflammation, and the drugs mentioned above are commonly used in the treatment of inflammation-associated disease because they can reduce the functions of caspase-1 and IL-1β. However, their applications in cancer therapy remain unknown. Thus, further investigations are warranted to characterize the antitumor activities of these potent inflammasome inhibitors.

**Conclusions**

The role of the inflammasome in cancer development has received increasing attention in recent years. During the progression of cancer, excessive inflammation stimulated by the inflammasome is the generally accepted hypothesis explaining the detrimental effect of inflammasomes on multiple forms of cancer. In the downstream course of the inflammasome pathway, IL-1β and IL-18 are activated by caspase-1 to generate an inflammatory response. Therefore, drugs that can downregulate the functions of these cytokines seem to have therapeutic activities in inflammation-associated diseases.

In various in vitro experiments, inflammasome inhibitors have been shown to attenuate the proliferation and invasion of cancer cells. However, their antitumor activities are limited to specific types of cancer. In terms of practical applications, the clinical trials studying inflammasome inhibitors have mainly focused on multiple myeloma, in which thalidomide and anakinra are well studied. Otherwise, inflammasome inhibitors are mostly utilized in inflammatory diseases such as osteoarthritis, rheumatoid arthritis, and colon colitis. Considering the limited application of inflammasome inhibitors in cancer treatment, we are looking forward to more broad-spectrum
and effective antitumor drugs. Several of the inflammasome inhibitors detailed above have been demonstrated to have the function of reducing inflammatory responses, indicating that inflammasome inhibitors could be novel candidates for the treatment of malignancies in which inflammation is involved as a major contributor.

The correlation between inflammasomes and cancer provides a promising approach for cancer therapy. The contrasting roles of inflammasomes in different cancers suggest the need for specific strategies when inhibitors are applied in cancer treatment. However, the inappropriate administration of inflammasome inhibitors might result in the repression of antitumor immunity and enhanced infection susceptibility and deterioration in autoinflammatory diseases. Consequently, the application of inflammasome inhibitors must be tailored to the specific type of cancer, and further studies are warranted to characterize the antitumor effects of these drugs.

Acknowledgements
Not applicable

Authors’ contributions
All authors have contributed to the preparation of this manuscript. All authors have read and approved the manuscript.

Funding
National Natural Science Youth Foundation of China (81602027); Youth Foundation of Xiangya Hospital Central South University (2015Q01); Natural Science Foundation General Program of Hunan Province (2018JJ3721); Project of scientific research plan of Hunan Provincial Health Commission (C2019185); Clinic and Rehabilitation research foundation of Sinobioway group (xywm2015I37)

Availability of data and materials
Not applicable

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

References
1. Martinson F, Burns K, Tschopp J. The inflammasome: a molecular platform for triggering activation of inflammatory caspases and processing of pro-Il-1β. Mol Cell. 2002;10(2):417–26.
2. Daguri M, Skeldon A, Saleh M. The inflammasome: in memory of Dr. Jurk Tschopp. Cell Death Differ. 2012;19(15):–12.
3. Ballinelli F, Coussens LM. Cancer: an inflammatory link. Nature. 2004;431(7007):405–6.
4. de Visser KE, Eichten A, Coussens LM. Paradigmatic roles of the immune system during cancer development. Nat Rev Cancer. 2006;6(1):24–7.
5. Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor microenvironment. Nat Immunol. 2013;14(10):1014–22.
6. Kantono M, Guo B. Inflammasomes and cancer: the dynamic role of the inflammasome in tumor development. Front Immunol. 2017;8:1132.
7. Chavarria-Smith J, Mitchell PS, Ho AM, Daugherty MD, Vance RE. Functional and evolutionary analyses identify proteolysis as a general mechanism for NLRP1 inflammasome activation. PLoS Pathog. 2016;12(12):e1006052.
8. Yuan F, Kolb R, Pandey G, Li W, Sun L, Liu F, et al. Involvement of the NLRC4 inflammasome in diabetic nephropathy. PLoS One. 2016;11(10):e0164135.
9. Broz P, von Moltke J, Jones JW, Vance RE, Monack DM. Differential requirement for Caspase-1 autopyroptosis in pathway-induced cell death and cytokine processing. Cell Host Microbe. 2010;8(6):471–83.
10. Jin T, Perry A, Smith P, Jiang J, Xiao TS. Structure of the absent in melanoma 2 (AIM2) pyrin domain provides insights into the mechanisms of AIM2 autoinhibition and inflammasome assembly. The Journal of biological chemistry. 2013;288(19):13225–35.
11. Girihringelli F, Apestoh L, Tesniere A, Aymetic L, Ma Y, Ortiz C, et al. Activation of the NLRP3 inflammasome in dendritic cells induces IL-1β-dependent adaptive immunity against tumors. Nat Med. 2009;15(10):1170–8.
12. Sutterwala FS, Haasen K, Cassel SL. Mechanism of NLRP3 inflammasome activation. Ann N Y Acad Sci. 2014;1319:82–95.
13. Malozowski S, Sahlroot JT. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med. 2007;357(3):302–3 author reply 3.
14. So A, De Smedt T, Revaz S, Tschopp J. A pilot study of IL-1 inhibition by anakinra in acute gout. Arthritis Res Ther. 2007;9(2):R28.
15. Menu P, Vincent JE. The NLRP3 inflammasome in health and disease: the good, the bad and the ugly. Clin Exp Immunol. 2011;156(1):1–15.
16. Lamkanfi M. Emerging inflammasome effector mechanisms. Nat Rev Immunol. 2011;11(3):213–20.
17. Rathanam VA, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. Nat Immunol. 2012;13(4):333–42.
18. Wu D, Pan P, Su X, Zhang L, Qin Q, Tan H, et al. Interferon regulatory factor-1 mediates alveolar macrophage pyroptosis during LPS-induced acute lung injury in mice. Shock. 2016;46(3):329–38.
19. Garaude J, Kent A, van Rooijen N, Blander JM. Simultaneous targeting of toll- and nod-like receptors induces effective tumor-specific immune responses. Sci Transl Med. 2012;4(120):120ra16.
20. Fernandes-Alnemri T, Kang S, Anderson C, Sagara J, Fitzgerald KA, Alnemri ES. Cutting edge: Toll-like receptor 3 activation triggers production of interferon-alpha in monocytes and macrophages. J Immunol. 2002;169(7):3759–62.
21. Kayagaki N, Warming S, Lamkanfi M, Vande Walle L, Louie S, Dong J, et al. Critical role of caspase-11 in pyroptosis induced by cytosolic DNA. Cell. 2013;145(3):480–9.
22. de los Santos E, Ploegh HL, Harder JM. Inflammasome involvement in fungal infection. Curr Opin Immunol. 2018;51:42–9.
23. Py BF, Kim MS, Vakifahmetoglu-Noberg H, Yuan J. Deubiquitination of NLRP3 inflammasome. J Immunol. 2012;189(1):355–62.
24. Rathinam VA, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. Nat Immunol. 2012;13(4):333–42.
25. van der Linden B, van der Velden P, de Loo C, Daha MR, Breiteneder H. Inflammasome activation upon infection with Leishmania donovani. PLoS Pathog. 2013;9(6):e1003374.
26. Datta P, Iiyama H, Yoshida M, Tsujinaka M, Takemura Y. The role of inflammasome in the defense of host cells against bacterial pathogens. Cell Physiol Biochem. 2016;38(5):1528–40.
27. Rehmanuddin K, Mohammadi M, Rhee JS, Stein DP, Schröder T. The receptors of the NLRP3 inflammasome in health and disease. Front Immunol. 2017;8:1132.
28. Py BF, Kim MS, Vakifahmetoglu-Noberg H, Yuan J. Deubiquitination of NLRP3 inflammasome. J Immunol. 2012;189(1):355–62.
Kolb R, Phan L, Borcherding N, Liu Y, Yuan F, Janowski AM, et al. Obesity-induced mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity. 2012;36(3):401–14.

Subramanian N, Natarajan K, Clanworth MJ, Wang Z, Germain RN. The adaptors MAVS promote NLRP3 mitochondrial localization and inflammasome activation. Cell. 2013;153(2):348–61.

Germo G, Allavara P, Mantovani A. Cytokines as a key component of cancer-related inflammation. cytokine. 2008;43(3):374–9.

Kolb R, Liu GH, Janowski AM, Suttenthaler FS, Zhang W. Inflammasomes in cancer: a double-edged sword. Protein Cell. 2014;5(1):12–20.

Williams TM, Leeth RA, Rothschild CD, Coutemars-Ort Sl, McDonal Dk, Simmons AE, et al. The NLRP1 inflammasome attenuates colitis and colitis-associated colorectal cancer by the inflammatory caspases. Immunity. 2010;32(3):367–78.

Allen IC, TeKippe EM, Woodford RM, Unrion JM, Hohl EK, Rogers AB, et al. The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colon cancer-associated inflammation. J Exp Med. 2010;207(5):1045–56.

Dupaul-Chicoine J, Arabzadeh A, Dagenais M, Champagne C, Rouleau J, Charron L, et al. IL-18 suppresses NK cell-mediated responses to carcinogen-induced tumors and metastases. Cancer Res. 2012;72(22):5721–32.

Zhou M, Jin C, Yang Y, Wang K, Zhou Y, Zhou Y, et al. AIM2 promotes non-small-cell lung cancer cell growth through inflammasome-dependent pathway. J Cell Physiol. 2019.

Bent SK, Yang L, Sinha P, Clements VK, Leips J, Ostrand-Rosenberg S. Reduced inflammation in the tumor microenvironment delays the accumulation of myeloid-derived suppressor cells and limits tumor progression. Cancer Res. 2007;67(20):10019–26.

Salcedo R, Worschech A, Cardone M, Jones Y, Gyulai Z, Dai RM, et al. MyD88-mediated signaling prevents development of adenocarcinomas of the colon: role of interleukin 18. J Exp Med. 2010;207(8):1625–36.

Harrison OJ, Srinivasan N, Pott J, Sciering C, Krausgaber T, Löttke NE, et al. Epithelial-derived IL-18 regulates TH17 cell differentiation and Foxp3+ Treg cell function in the intestine. Mucosal Immunol. 2015;8(6):1226–36.

Dahut WL, Gulley JL, Arlen PM, Liu Y, Fedenko KM, Steinberg SM, et al. Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. J Clin Oncol. 2004;22(13):2532–9.

Singhal S, Mehta J, Desikan R, Ayers D, Robinson P, Edelmann P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med. 1999;341(21):1565–71.

Tiozzo PL, Aldrich W. Effects of interleukin-1 receptor antagonist and chemotherapy on host-tumor interactions in established melanoma. Anticancer Res. 2010;30(2):345–54.

Hollen I, Leffey DV, Francis SE, Rennicks S, Bradbury S, Coleman RE, et al. IL-1 δ drives breast cancer growth and bone metastasis in vivo. Oncotarget. 2016;7(4):5571–84.

Luo H, Gao L, Muyldemans SF, Zeldennrunst SR, Dispensiere A, Gertz MA, Witzig TE, et al. Induction of a chronic disease state in patients with smoldering or indolent multiple myeloma by targeting interleukin 1(beta)-induced interleukin 6 production and the myeloma proliferative component. Mayo Clin Proc. 2009;84(11):114–22.

Qiu Y, Li WH, Zhang HQ, Liu Y, Tian XX, Fang WG. P2X7 mediates ATP-driven invasiveness in prostate cancer cells. PLoS One. 2014;9(12):e114371.

Gianuazzo A, Pedersen SF, Novak I. The P2X7 receptor regulates cell survival, migration and invasion of pancreatic ductal adenocarcinomas. Mol Cancer. 2015;14:203.

Gianuazzo A, Saccomano M, Napp J, Elleegaard M, Alves F, Novak I. Targeting of the P2X7 receptor in pancreatic cancer and stellite cells. Int J Cancer. 2016;139(11):2540–52.

Adinolfi E, Cirillo M, Woltersdorf R, Falzoni S, Chiozzi P, Pellegratti P, et al. Tropic activity of a naturally occurring truncated isoform of the P2X7 receptor. FASEB J. 2010;24(9):3393–404.

Farrell AW, Gadeck F, Popovac A, Wang B, Jallian I, Ransom M, et al. P2X7 receptor activation induces cell death and CD23 shedding in human RPMI 8226 multiple myeloma cells. Biochim Biophys Acta. 2010;1800(11):1173–82.

Bae JF, Lee SW, Shin YH, Lee JH, Jahng JW, Park K. P2X7 receptor and NLRP3 inflammasome activation in head and neck cancer. Oncotarget. 2017;8(30):48972–82.

Fei Q, Xiao J, Hu B, Sun N, Wei Y, Zhu J. High expression of P2X7R is an independent postoperative indicator of poor prognosis in colorectal cancer. Human Pathol. 2017;64:661–8.

Gilbert SM, Gidley Baird A, Glazer S, Barden JA, Glazer A, Tch LG, et al. A phase I clinical trial demonstrates that nP2X7-targeted antibodies provide a novel, safe and tolerable topical therapy for basal cell carcinoma. Br J Dermatol. 2017;177(1):117–24.

Sohma I, Fujimura Y, Sugita Y, Yoshio A, Shirakawa M, Moon JH, et al. Parthenolide, an NF-kappaB inhibitor, suppresses tumor growth and enhances response to chemotherapy in gastric cancer. Cancer Genomics Proteomics. 2011;8(1):39–47.

Kim SL, Trang KT, Kim SH, Kim JH, Lee SO, Lee ST, et al. Parthenolide suppresses tumor growth in a xenograft model of colorectal cancer cells by inducing mitochondrial dysfunction and apoptosis. Int J Oncol. 2012;41(4):1547–53.

Liu JW, Cai MX, Xin Y, Wu QS, Ma J, Yang P, et al. Parthenolide induces proliferation inhibition and apoptosis of pancreatic cancer cells in vitro. J Exp Clin Cancer Res. 2010;29:108.
72. Zhang R, Zhao J, Xu J, Jiao DX, Wang J, Gong QZ, et al. Androgapholide suppresses proliferation of human colon cancer SW620 cells through the TLR4/NF-kappaB/MAPK signaling pathway. Oncol Lett. 2017;14(4):4305–10.
73. Su M, Qin B, Liu F, Chen Y, Zhang R. Androgapholide enhanced S- fluorouracil-induced antitumor effect in colorectal cancer via inhibition of c-MET pathway. Drug Des Devel Ther. 2017;11:3333–41.
74. Guo W, Sun Y, Liu W, Wu X, Guo L, Cal P, et al. Small molecule-driven mitophagy-mediated NLPR3 inflammasome inhibition is responsible for the prevention of colitis-associated cancer. Autophagy. 2014;10(6):972–85.
75. Zhai Z, Qu X, Li H, Yuan Z, Yan W, Liu G, et al. Androgapholide prevents human breast cancer-induced osteosclerotic bone loss via attenuated RANKL signaling. Breast Cancer Res Treat. 2014;141(3):33–45.
76. Zhai Z, Xu X, Ju H, Dayang Z, Yan W, Liu G, et al. Inhibition of MDA-MB-231 breast cancer cell migration and invasion activity by androgapholide via suppression of nuclear factor-kappaB-dependent matrix metalloproteinase-9 expression. Mol Med Rep. 2015;11(2):1391–45.
77. Gao H, Wang J. Androgapholide inhibits multiple myeloma cells by inhibiting the TLR4/NF-kappaB signaling pathway. Mol Med Rep. 2016;13(2):1827–32.
78. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ. Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet. (London, England). 2017; 390(10105):1833–42.
79. Miller MT. Thalidomide embryopathy: a model for the study of congenital anomalies in families. Annu Rev Immunol. 2009;27:519–53.
80. Peng HL, Yi YF, Zhou SK, Xie SS, Zhang GS. Thalidomide effects in patients with myelodysplastic syndromes. Blood. 2001;97(5):1427–30.
81. Endothelial-mesenchymal transition in normal human esophageal epithelial cells cocultured with esophageal adenocarcinoma cells: role of IL-1beta and TGF-beta2. Am J Physiol Cell Physiol. 2014;307(3):C589–77.
82. Singh JA, Hossain A, Tanjong Ghogomu E, Kotb A, Christensen R, Muddano AS, et al. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2016;5:CD012183.
83. Agrawal A, Gartland A. P2X7 receptor antagonism in the treatment of cancers. Expert Opin Investig Drugs. 2011;20(7):875–80.
84. Lopez-Castejon G, Theaker J, Pelegrin P, Clifton AD, Braddock M, Surprenant A. P2X7 receptor-mediated release of cathepsins from macrophages is a cytokine-independent mechanism potentially involved in joint diseases. J Immunol. 2010;184(4):2611–9.
85. Gu BJ, Wiley JS. Rapid ATP-induced release of matrix metalloproteinase 9 is mediated by the P2X7 receptor. Blood. 2006;107(12):4946–53.
86. Hill LM, Gavala ML, Lenertz LY, Bertics PJ. Extracellular ATP may contribute to tissue repair by rapidly stimulating pulsatile receptor ATP-dependent vascular endothelial growth factor release from primary human monocytes. J Immunol. 2010;185(5):3028–34.
87. Kwok BH, Koh B, Ndubuisi MI, Elofsson M, Crews CM. The anti-inflammatory natural product parthenolide from the medicinal herb Feverfew directly binds to and inhibits IkappaB kinase. Chem Biol. 2001(8):759–66.
88. Nening SE, Schank JR. The role of NFkB in drug addiction: beyond inflammation. Alcohol Alcohol. 2017;52(2):172–9.
89. Zhang S, Lin ZN, Yang CF, Shi X, Ong CN, Shen HM. Suppressed NF-kappaB regulated and sustained JNK activation contribute to the sensitization effect of parthenolide to TNF-alpha-induced apoptosis in human cancer cells. Carcinogenesis. 2004;25(11):1919–9.
90. Gopal TN, Chanchorn E, Van Dyke MW. Parthenolide promotes the ubiquitination of MDM2 and activates p53 cellular functions. Mol Cancer Ther. 2009;8(3):552–62.
91. Bhowmik S, Raza S, Bawa M, Kasza A, Bugno M, Kordula T. Parthenolide inhibits activation of signal transducers and activators of transcription (STATs) induced by cytokines of the IL-6 family. Biochem Biophys Res Commun. 2000;267(1):329–33.
92. Curry EA 3rd, Muny DJ, Yoder C, Fife K, Armstrong V, Nakshati H, et al. Phase I dose escalation trial of feverfew with standardized doses of parthenolide in patients with cancer. Invest New Drugs. 2004;22(3):299–305.
93. Guzman ML, Ross MI, Neelakantan S, Li X, Corbett CA, Hassane DC, et al. An orally bioavailable parthenolide analog selectively eradicate acute myelogenous leukemia stem and progenitor cells. Blood. 2007;110(3):4427–35.
94. Sur R, Martin K, Liebel F, Lyte P, Shapiro S, Southall M. Anti-inflammatory activity of parthenolide-depleted Feverfew (Tanacetum parthenium). Inflammopharmacology. 2009;17(1):42–9.
95. Lachmann HJ, Kone-Paut I, Kuenmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med. 2009;360(23):2416–25.
96. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119–31.
97. Cuzick J, Otto F, Baron JA, Brown PH, Burn J, Greenland P, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol. 2009;10(5):501–7.
98. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet (London, England). 2011;377(9765):31–41.
99. Chakravarti RN, Chakravarti D. Androgapholide, the active constituent of Andrographis paniculata Nees; a preliminary communication. Ind Med Res. 1951;18(3):96–7.
100. Bao Z, Guan S, Cheng C, Wu S, Wong SH, Kemeny DM, et al. A novel antiinflammatory role for androgapholide in asthma via inhibition of the nuclear factor-kappaB pathway. Am J Respir Crit Care Med. 2009;180(4):657–66.
101. Shi MD, HH Li, Lee YC, Chau JK, Lin RA, Chen JH. Inhibition of cell-cycle progression in human colorectal carcinoma Lovo cells by androgapholide. Chem Biol Interact. 2008;174(3):201–10.
102. Chang J, Zhang RM, Zhang Y, Chen ZB, Zhang ZM, Xu Q, et al. Androgapholide drop-pill in treatment of acute upper respiratory tract infection with external
wind–heat syndrome: a multicenter and randomized controlled trial. Zhong Xi Yi Jie He Xue Bao. 2008;6(12):1238–45.

116. Gabrielsen ES, Shukarian AK, Goukasov GL, Chandanian GL, Panossian AG, Wilkman G, et al. A double blind, placebo-controlled study of Andrographis paniculata fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis. Phytomedicine. 2002;9(7):589–97.

117. Riddle MC. Editorial: sulfonlureyas differ in effects on ischemic preconditioning—is it time to retire glyburide? J Clin Endocrinol Metab. 2003;88(2):528–30.

118. Serrano-Martín X, Payares G, Mendoza-Leon A. Glibenclamide, a blocker of K+(ATP) channels, shows antileishmanial activity in experimental murine cutaneous leishmaniasis. Antimicrobial agents and chemotherapy. 2006;50(12):4214–6.

119. Tamura K, Ishikawa G, Yoshiie M, Ohneda W, Nakai A, Takeshita T, et al. Glibenclamide inhibits NLRP3 inflammasome-mediated IL-1beta secretion in human trophoblasts. J Pharmacol Sci. 2017;135(2):89–95.

120. Koh GC, Maude RR, Schreiber MF, Limmathurotsakul D, Wiersinga WJ, Wuthiekanun V, et al. Glyburide is anti-inflammatory and associated with reduced mortality in melioidosis. Clin Infect Dis. 2011;52(6):717–25.

121. Marchetti C, Chojnacki J, Toldo S, Mezzaroma E, Tranchida N, Rose SW, et al. A novel pharmacologic inhibitor of the NLRP3 inflammasome limits myocardial injury after ischemia-reperfusion in the mouse. J Cardiovasc Pharmacol. 2014;63(4):316–22.

122. Coll RC, Robertson AB, Chae JJ, Higgins SC, Muñoz-Planillo R, Inserna MC, et al. A small molecule inhibitor of the NLRP3 inflammasome is a potential therapeutic for inflammatory diseases. Nature Medicine. 2015;21(9):248.

123. Coll RC, Robertson A, Butler M, Cooper M, O'Neill LA. The cytokine release inhibitory drug CRID3 targets ASC oligomerisation in the NLRP3 and AIM2 inflammasomes. PLoS One. 2011;6(2):e19539.

124. Laliberte RE, Perregaux DG, Hoth LR, Roos PJ, Jordan CK, Peese KM, et al. Targeting caspase-1 inhibitors as novel anti-inflammatory drugs. Expert Opin Investig Drugs. 2014;63(4):316–22.

125. Labiberté RE, Perregaux DG, Hoth LR, Roos PJ, Jordan CK, Peese KM, et al. Gilthathione s-transferase omega 1-1 is a target of cytokine release inhibitory drugs and may be responsible for their effect on interleukin-1beta proinflammatory processing. J Biol Chem. 2003;278(19):16567–78.

126. Perera AP, Fernando R, Shinde T, Gundamaraju R, Southam B, Sohal SS, et al. MCC950, a specific small molecule inhibitor of NLRP3 inflammasome attenuates colonic inflammation in spontaneous colitis mice. Sci Rep. 2018;8(1):8618.

127. Randle JC, Harding MW, Ku G, Schönhartig M, Kunkel R. ICE/Caspase-1 inhibitors as novel anti-inflammatory drugs. Expert Opin Investig Drugs. 2001;10(7):1307.

128. Ayala JM, Yamin TT, Egger LA, Chin J, Kostura MJ, Miller DK. IL-1 beta-converting enzyme is present in monocytic cells as an inactive 45-kDa precursor. J Immunol. 1994;153(6):2592.

129. Rontheim SR, Mumma A., Greenstreet T., Glackin PJ, van Ness K , March CJ, et al. Purification of interleukin-1 beta-converting enzyme, the protease that cleaves the interleukin-1 beta precursor. Arch Biochem Biophys. 1992;296(2):698–703.

130. Rudolph K, Gerwin N, Verzijl N, Kumar A, Pape D. IL-1beta secretase in human trophoblasts. J Pharmacol Sci. 2017;135(2):89–95.

131. Floris J, Noel A, Foveau B, Lynham J, LeBlanc C, LeBlanc AC. Caspase-1 inhibition alleviates cognitive impairment and neuropathology in an Alzheimer’s disease mouse model. Nat Commun. 2018;9(1):3916.

132. Yang XM, Downey JM, Cohen MV, Housley NA, Alvarez DF, Audia JP. The highly selective caspase-1 inhibitor VX-765 provides additive protection against myocardial infarction in rat hearts when combined with a platelet inhibitor. J Cardiovasc Pharmacol Ther. 2017;22(6):574–8.