Diverging inflammasome signals in tumorigenesis and potential targeting

Rajendra Karki and Thirumala-Devi Kanneganti *

Abstract | Inflammasomes are molecular platforms that assemble upon sensing various intracellular stimuli. Inflammasome assembly leads to activation of caspase 1, thereby promoting the secretion of bioactive interleukin-1β (IL-1β) and IL-18 and inducing an inflammatory cell death called pyroptosis. Effectors of the inflammasome efficiently drive an immune response, primarily providing protection against microbial infections and mediating control over sterile insults. However, aberrant inflammasome signalling is associated with pathogenesis of inflammatory and metabolic diseases, neurodegeneration and malignancies. Chronic inflammation perpetuated by inflammasome activation plays a central role in all stages of tumorigenesis, including immunosuppression, proliferation, angiogenesis and metastasis. Conversely, inflammasome signalling also contributes to tumour suppression by maintaining intestinal barrier integrity, which portrays the diverse roles of inflammasomes in tumorigenesis. Studies have underscored the importance of environmental factors, such as diet and gut microbiota, in inflammasome signalling, which in turn influences tumorigenesis. In this Review, we deliver an overview of the interplay between inflammasomes and tumorigenesis and discuss their potential as therapeutic targets.

Gut microbiota
The ecological community of microorganisms harboured in the gastrointestinal tract.

Department of Immunology, St. Jude Children's Research Hospital, Memphis, TN, USA.

**e-mail: thirumala-devi.kanneganti@stjude.org*

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Inflammasomes are macromolecular complexes that trigger central and rapid inflammatory responses to cytosolic insults. Inflammasome sensors are grouped on the basis of their structural features into nucleotide-binding oligomerization domain and leucine-rich repeat receptors (NLRs), absent in melanoma 2 (AIM2)-like receptors (ALRs) and the recently identified pyrin. The NLR family is subdivided into NLRPs or NLRCs on the basis of whether the amino terminus contains a pyrin domain (PYD) or a caspase activation and recruitment domain (CARD), respectively[1]. NLRP1 (mouse NLRP1b), NLRP3 and NLR family apoptosis inhibitory protein (NAIP)–NLRC4 are well-established NLRs for their ability to assemble inflammasomes[2,3]. Several other NLR sensors, including NLRP6, NLRP7, NLRP9, NLRP12, NLRC3 and NLRC5, and non-NLR sensors, such as interferon-γ (IFNγ)-inducible protein 16 (IFI16) and retinoic acid-inducible gene I, may form inflammasome complexes in context-dependent manners[4–6]. Inflammasomes are largely described in immune cells, such as macrophages and dendritic cells (DCs), but are also expressed and assembled in non-haematopoietic cells[4].

Previous studies have indicated that the inflammasome-dependent biological responses — both inflammation and cell death — regulate the pathogenesis of a broad range of diseases including obesity, diabetes, atherosclerosis, gout and ulcerative colitis[7]. Additionally, the complex roles of inflammasomes in tumorigenesis and antitumour immunity have been revealed over the past decade. The hallmarks of a tumour are determined by the central biological characteristics that tumours acquire during the multistep process of tumorigenesis[8]. Remarkably, inflammasome signalling is implicated in virtually every aspect of tumour development, performing either tumour-suppressive or pro-tumorigenic functions[9] (TABLE 1). In this Review, we describe the dynamic and divergent roles of inflammasome signalling in multiple tissues and organs, highlighting its major functions in shaping inflammatory responses, cellular proliferation and survival, immunosuppression, angiogenesis, metastasis and the gut microbiota, all of which are critical for modulating tumorigenesis. We also discuss recent advances made in translational research that motivate potential pharmacological approaches targeting the inflammasome in tumorigenesis.

Inflammasome activation

Upon sensing stimuli, inflammasome sensors generally recruit the common adaptor molecule apoptosis-associated speck-like protein containing a CARD (ASC), which forms a platform for the activation of caspase 1. Recruitment and oligomerization of these components by homotypic CARD–CARD or PYD–PYD interactions

Table 1 | **Diverse roles of inflammasomes across different cancers**

Cancer type	Animal model	In vitro systems
Lung cancer (implanted tumours)	• Rapid growth of LLC cells in mice transduced with human IL-1β-expressing vector[53] • Decreased lung metastases of B16F10 melanoma, RM-1 prostate and E0771 mammary adenocarcinoma cells in *Nlrp3*$^{-/-}$ mice[65] • Decreased lung metastases and tumour growth of B16 melanoma cells in *Il1b*$^{-/-}$ mice[58] or *Il18r*$^{-/-}$ mice[41] • Increased lung metastases of LLC cells in *Casp1*$^{-/-}$*Casp11*$^{-/-}$ mice[62] • Reduced tumour growth in nude mice injected with *Gsdmd*-silenced PC9 cells[39]	• Decreased proliferation and migration of *Nlrp3*-silenced, caspase 1-inhibited and IL-18BP-added A549 cells[173] • Augmentation of IL-1α release from AIM2-activated lung tumour-associated pDCs[49] • Decreased viability and increased apoptosis in *Gsdmd*-silenced PC9, H1703 and H1975 cells[39]
Breast cancer (implanted tumours)	• Reduced tumour growth of Py8119 cells in *Il1b*$^{-/-}$ mice[129] • Reduced tumour growth of E0771, PyT8 or MDA-MB-231 cells in *Casp1*$^{-/-}$ and *Nlrp3*$^{-/-}$ mice[64] • Reduced tumour growth of MDA-MB-435 in mice treated with SN2 liposome with pCMV-Tag-AIM2[107] • Reduced tumour progression in 4T1 tumour-bearing mice treated with IL-1R antibody[48] • Retarded tumour growth in E0771 cell-bearing mice treated with anakinra[48] • Reduced tumour growth of Py8119 or E0771 cells in diet-induced obese *Casp1*$^{-/-}$, *Casp11*$^{-/-}$ or *Nlrc4*$^{-/-}$ mice[129]	• Increased migration and invasion of IL-1β-treated BT474 cells[72] • Increased migration of IL-18-treated and decreased migration of *Il18* -silenced MCF-7 cells[73] • Decreased viability and colony-forming ability of *Aim2*-overexpressing MCF-7, MDA-MB-231, MDA-MB-435 and MDA-MB-453 cells[107,108]
Fibrosarcoma	• Reduced MCA-induced tumour incidence in *Nlrp3*$^{-/-}$, *Casp1*$^{-/-}$ and *Il1r*$^{-/-}$ mice[65] • Reduced tumour growth in IL-18-injected mice after implantation of T241 cells[174]	NA
Gastric cancer	• Increased gastric cancer in *IL1B* transgenic mice infected with *Helicobacter felis*[33] • Reduced gastric preneoplasia in *Il1r*$^{-/-}$ mice infected with *Helicobacter felis*[175] • Reduced tumour volume of *Il18*-silenced gastric cancer cells in nude mice[42] • Reduced tumour incidence in *gp130*$^{F/F}$*Asc*$^{-/-}$ or *gp130*$^{F/F}$*Il18*$^{-/-}$ mice[32] • Decreased tumour growth of *Gsdmd*-expressing BGC-823 cells in nude mice[176]	• Suppressed colony formation of AGS and MKN1 cells treated with IL-18 neutralizing antibody[32] • Suppressed colony formation in *Asc*$^{-/-}$ and *Casp1*$^{-/-}$ AGS cells[32] • Decreased proliferation and colony formation in *Gsdmd*-overexpressing BGC-823 cells, and increased proliferation in *Gsdmd*-silenced BGC-823 cells[176]
Hepatic cancer (implanted tumours)	• Regression of CT26 tumours in the livers of wild-type mice after *Il18* gene transfer[177] • Decreased hepatic metastases of B16 melanoma cells in mice injected with IL-18BP[61] • Reduced tumour incidence in DEN-treated *Casp1*$^{-/-}$ and *Aim2*$^{-/-}$ mice[178] • Decreased hepatic metastases of B16 melanoma in *Il1b*$^{-/-}$ and *Casp1*$^{-/-}$*Casp11*$^{-/-}$ mice[57] • Increased metastases in mice injected with *Aim2*-silenced HCC cells[179] • Decreased MC38 metastatic tumours in the livers of *Nlrp3*$^{-/-}$ mice[63] • Increased MC38 metastatic tumours in the livers of *Casp1*$^{-/-}$*Casp11*$^{-/-}$, *Nlrp3*$^{-/-}$, *Il18*$^{-/-}$ and *Il18r*$^{-/-}$ mice[62]	Increased migration and invasion of *Aim2*-silenced HCC cells[179]
Colon cancer (AOM and/or DSS)	• Increased tumours in the colons of *Nlrp3*$^{-/-}$ (REFS[77,78]), *Aim2*$^{-/-}$ (REFS[79,80]), *Nlrc4*$^{-/-}$ (REFS[81,82]), *Naip1–Naip6*$^{-/-}$ (REF.[101]), *Nlrp1b*$^{-/-}$ (REF.[76]), *Nlrp6*$^{-/-}$ (REFS[82,180,181]), *Nlrp12*$^{-/-}$ (REFS[114,115]), *Pyrin*$^{-/-}$ (REF.[83]), *Asc*$^{-/-}$ (REFS[76–79,82]), *Casp1*$^{-/-}$ (REFS[77,81]), *Il18*$^{-/-}$ (REFS[78,87]) and *Il18r*$^{-/-}$ (REF.[87]) mice • Decreased tumours in the colons of IL-18-injected *Casp1*$^{-/-}$ (REF.[78]), *Pyrin*$^{-/-}$ (REF.[83]) or *Il18*$^{-/-}$ (REF.[83]) mice • Decreased tumours in the colons of *Casp1*$^{-/-}$ (REF.[182]) and *Nlrp3*^{R258W} mice[96] • Decreased tumours in the colons of IL-1RA-injected wild-type mice[183] • Increased tumours in the colons of IL-1β-treated complement-deficient mice[184] • More tumours in the colons of *Ptpn2*$^{-/-}$ mice treated with a vaccine against IL-1β and in *Ptpn2*$^{-/-}$*Asc*$^{-/-}$ mice[97]	• Increased proliferation and invasion of HT29, Caco-2, HCA7 and HCT116 cells co-cultured with IL-1β-treated normal or cancer-associated fibroblasts[185] • Decreased survival of *AIM2*-expressing HCT116 cells[103] • Decreased migration and invasion of *Nlrp3*-silenced HCT116, HT29 and SW620 cells[75]
Prostate cancer	Decreased metastatic lesions in bones of wild-type mice injected with *Il1b*-silenced PC-3 cells, and increased metastatic lesions in bones of wild-type mice injected with IL-1β-overexpressing DU-145 cells[186]	Increased migration of IL-1β-stimulated PC-3 cells[187]
Glioblastoma	• Reduced growth of 9L cells in wild-type mice or wild-type rats inoculated with BMSCs expressing IL-18 (REFS[188,189]) • Increased survival and decreased tumour size in wild-type rats following injection of IL-18-transduced C6 glioma cells[190] • Decreased tumour size in mice injected with SR-B10 cells following administration of recombinant IL-18 (REF.[191]) • Reduced tumour growth of GL261 and U87 cells in *Nlrp3*-silenced mice following ionizing radiation treatment[192]	• Increased proliferation, migration and invasion of IL-1β-treated U87 and U251 cells[193] • Increased apoptosis of IL-1β-treated hypoxic U87 cells[194] • Decreased viability and increased apoptosis of 9L glioma cells co-cultured with BMSCs expressing IL-18 (REFS[188,189])

Table 1 (cont.) | **Diverse roles of inflammasomes across different cancers**

Cancer type	Animal model	In vitro systems
Skin cancer and/or melanoma	• Delayed tumour onset in 3-MCA-treated *Il1b*$^{-/-}$ mice[195] • Reduced tumour growth in mice injected with *Nlrp1b*-silenced 1205Lu cells[196] • Reduced tumour incidence in DMBA-treated and/or TPA- treated *Il1r*$^{-/-}$ and *Casp1*$^{-/-}$ mice[99] • Reduced tumour incidence in LysM-*Asc*$^{-/-}$ mice, and increased tumour incidence in K14-*Asc*$^{-/-}$ mice after DMBA and/or TPA treatment[99] • Reduced papilloma lesions in *Nlrp3*$^{-/-}$ mice[197] • Increased tumour size in *Nlrc4*$^{-/-}$ mice challenged with B16F10 cells[100] • Reduced B16 tumour growth in chimeric wild-type mice adoptively transferred with *Casp1*$^{-/-}$ BMCs[198]	• Increased proliferation of IL-18-treated B16M, A375, HMB2, VUP, SK23 and MJM melanoma cells[61] • Decreased viability and increased apoptosis of *Nlrp1b*-silenced WM115, 1205Lu and Hs294T cells[196]
Squamous cell carcinoma	• Reduced tumour burden in the heads and necks of NLRP3 inhibitor (MCC950)-treated *Tgfbr1*$^{-/-}$*Pten*$^{-/-}$ mice[199] • Delayed onset and smaller tumour area in the tongues of 4-NQO-administered and 5-FU-treated *Nlrp3*$^{-/-}$ and *Casp1*$^{-/-}$ mice[158] • Reduced tumour growth in SCID mice injected with *Aim2*-silenced UT-SCC7 cells[38] • Reduced tumour growth in nude mice injected with *Nlrp3*-silenced WSU-HN6 cells[68]	• More colony formation in LPS + ATP-treated CAL27 cells[199] • Reduced viability and increased apoptosis of *Nlrp3*-silenced WSU-HN6 and CAL27 cells treated with 5-FU[158] • Reduced viability and increased apoptosis of *Aim2*-silenced UT-SCC7 cells[38] • Increased proliferation and migration of IL-1β-treated DOK and TW2.6 cells[200]
Pancreatic cancer	• Reduced pancreatic neoplasia and improved survival of *Aim2*-deficient KC*Pink1*$^{-/-}$ and KC*Park2*$^{-/-}$ mice[50] • Delayed malignant progression and extended survival in *Nlrp3*$^{-/-}$ KC mice[47] • Reduced PDA tumour growth in the pancreata of *Nlrp3*$^{-/-}$, *Asc*$^{-/-}$ and *Casp1*$^{-/-}$ mice[47] • Reduced Panc02 tumour growth in chimeric wild-type mice adoptively transferred with *Casp1*$^{-/-}$ BMCs[198]	NA
Haematopoietic neoplasms	Delayed multiple myeloma progression and prolonged survival in *Nlrp1*$^{-/-}$ and *Il18*$^{-/-}$ mice challenged with myeloma cell lines[51]	Enhanced proliferation of IL-18-treated Pfeiffer cells[201]
Malignant mesothelioma	Delayed onset and reduced tumour incidence in *Asc*$^{-/-}$ mice[202]	NA

The cell lines listed in the table include melanoma (A375, B16F10, HMB2, VUP, SK23, MJM, WM115, 1205Lu and Hs294T), prostate cancer (RM-1, PC3-ML and DU145), breast cancer (E0771, Py8119, PyT8, MDA-MB-231, MDA-MB-435, MDA-MB-453, 4T1, BT474 and MCF-7), lung cancer (PC, A549, H1703 and H1975), fibrosarcoma (T241), gastric cancer (BGC-823, AGS and MKN1), colon cancer (CT26, MC38, HCT116, HPCC, HT29, Caco-2, HCA7 and SW620), liver cancer (Hepa1-6), glioma (9L, C6, SR-B10, GL-261, U87, T98G and U251), squamous cell carcinoma (UT-SCC7, WSU-HN6, CAL27, DOK and TW2.6) and pancreatic cancer (Panc02) cell lines. 3-MCA, methylcholanthrene; 4-NQO, 4-nitroquinoline 1-oxide; 5-FU, 5-fluorouracil; AIM2, absent in melanoma 2; AOM, azoxymethane; BMCs, bone marrow cells; BMSCs, bone marrow stem cells; DEN, *N*,*N*-diethylnitrosamine; DSS, dextran sodium sulfate; HCC, hepatocellular carcinoma; IL-1β, interleukin-1β; IL-18BP, interleukin-18 binding protein; IL-1R, interleukin-1 receptor; IL-1RA, interleukin-1 receptor antagonist; KC, *Pdx1*^{cre}*Kras*$^{G12D/+}$; LLC, Lewis lung carcinoma; LPS, lipopolysaccharide; MCA, methylcholanthrene; NA, not available; PDA, pancreatic ductal adenocarcinoma; pDCs, plasmacytoid dendritic cells; SCID, severe combined immunodeficiency.

are the basis of inflammasome assembly, which is followed by proximity-induced autoprocessing of caspase 1. ASC is a bipartite protein containing both a PYD and a CARD. PYD-containing AIM2, NLRP3 and pyrin interact with the CARD of caspase 1 via ASC, whereas CARD-containing NLRP1b and NLRC4 do not necessarily require ASC for their interaction with caspase 1 (REF.[4]). Active caspase 1 proteolytically cleaves the pro-inflammatory cytokines pro-interleukin-1β (pro-IL-1β) and pro-IL-18 into bioactive IL-1β and IL-18 (REF.[2]). Similarly, active caspase 1 cleaves gasdermin D (GSDMD), which subsequently forms pores in the cell membrane, thereby allowing the secretion of mature IL-1β and IL-18 as well as certain damage-associated molecular patterns (DAMPs) (FIG. 1). IL-1β can pass through the GSDMD pore in the absence of membrane rupture, suggesting that pyroptosis is not a prerequisite for the release of this cytokine[10]. Moreover, vesicular release has been described as an alternative mechanism for slow release of mature IL-1β; however, effective and robust release of IL-1β depends on GSDMD[11,12]. Unlike in myeloid cells, where caspase 1 is required for processing of IL-18 and IL-1β, it appears that caspase 1-independent IL-18 processing by caspase 4 occurs in human intestinal epithelial cells[13]. These distinctive features suggest mechanistic differences in the processing and release of cytokines between cell types.

There are two distinct molecular mechanisms governing the ability of different inflammasome sensors to initiate inflammasome assembly. NLRP1, NLRP3 and pyrin assemble inflammasomes without directly binding ligands, but caspase 11 (the mouse analogue of caspase 4 and caspase 5 in humans and a sensor for non-canonical NLRP3), AIM2 and NAIPs directly bind to their ligands for inflammasome activation[7].

Non-ligand binding sensors

NLRP1. Human NLRP1 has three paralogues, NLRP1a–NLRP1c, in mice. Unlike human NLRP1, mouse NLRP1 lacks PYD. NLRP1b responds to the lethal toxin of *Bacillus anthracis*. Any protease that induces amino-terminal proteolytic cleavage at the amino terminus or the function to find (FIIND) domain of NLRP1 can activate this inflammasome[14,15] (FIG. 1a). It has been proposed that lethal factor-mediated cleavage relieves intramolecular autoinhibition or induces conformational changes that subsequently lead to oligomerization of the receptor.

Pyroptosis
An inflammatory and lytic form of cell death mediated by inflammatory caspases.

Canonical NLRP3. Although no direct ligands of NLRP3 have been identified yet, it is known to respond to cellular aberrations characterized by lysosomal rupture, potassium efflux, mitochondrial DNA disruption, calcium influx or a decrease in cellular cAMP levels, all of which are caused by various pathogen-associated molecular patterns (PAMPs) and DAMPs, including toxins, pathogens, crystalline substances and metabolites[7]. Serine/threonine-protein kinase NEK7 and MAPK transforming growth factor-β (TGFβ)-activated kinase 1

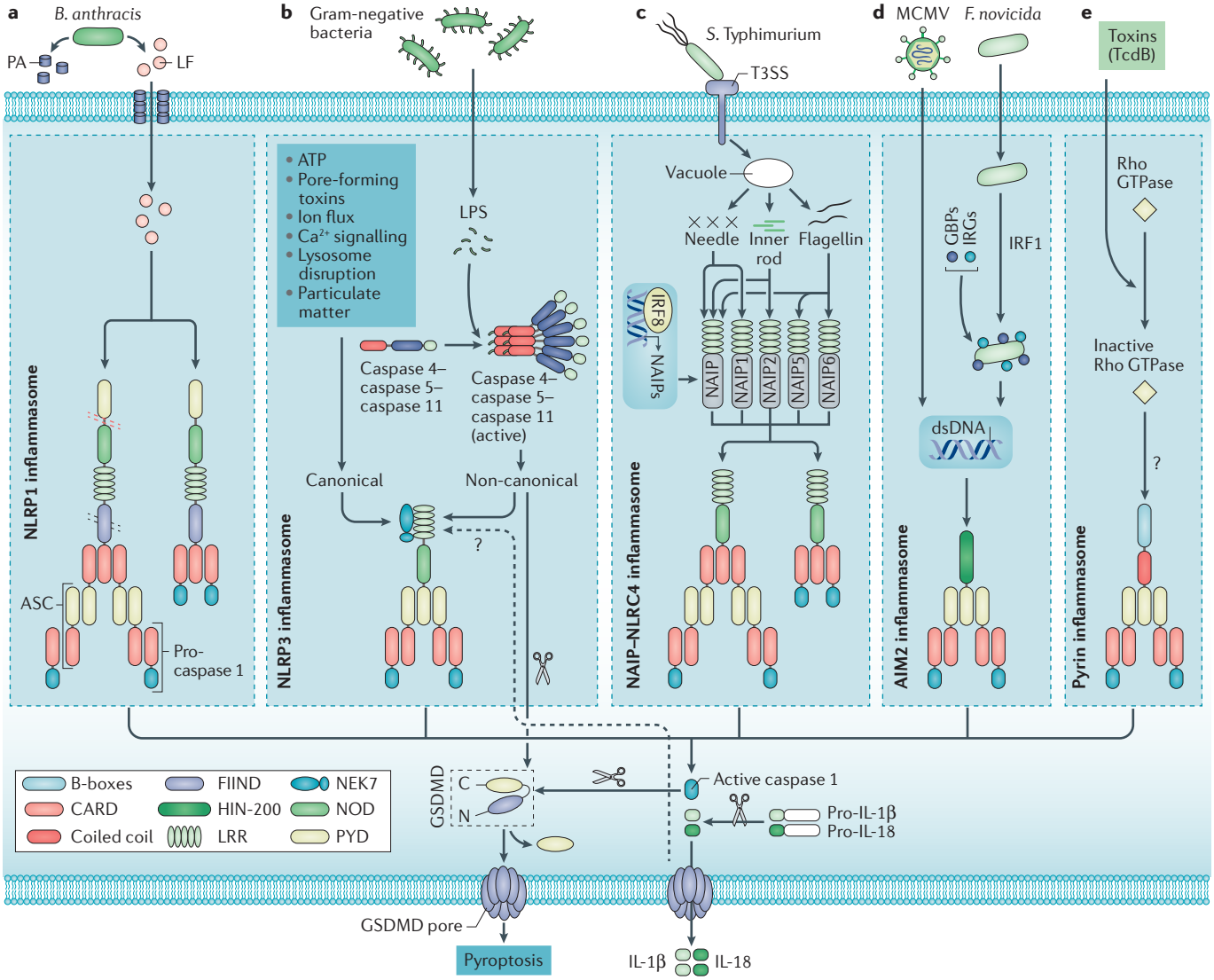

Fig. 1 | **Diverse mechanisms of inflammasome activation. a** | *Bacillus anthracis* toxin, which contains protective antigen (PA) and lethal factor (LF), activates the NLRP1 inflammasome by inducing cleavage at the amino-terminal linker region (red dotted line). PA forms pores in the host cell membrane, which is used by LF to enter the cell. Auto-proteolytic cleavage at the function to find (FIIND) domain (black dotted line) has also been observed. Caspase 1 is recruited into the complex via apoptosis-associated speck-like protein containing a CARD (caspase activation and recruitment domain) (ASC) or by direct association with NLRP1 through CARD–CARD interactions. **b** | The NLRP3 inflammasome is activated by various pathogen-associated molecular patterns and damage-associated molecular patterns. Serine/threonine-protein kinase NEK7 is an upstream activator of NLRP3 inflammasome assembly. Non-canonical NLRP3 inflammasome activation induced by cytosolic lipopolysaccharide (LPS) is dependent on caspase 11, which is the mouse analogue of human caspase 4 and caspase 5. Caspase 11 cleaves the amino-terminal domain of gasdermin D (GSDMD) to induce pyroptosis. **c** | Bacterial flagellin is sensed by NLR family apoptosis inhibitor protein 5 (NAIP5) and NAIP6, and type 3 secretion system (T3SS) components, needle and inner rod, are sensed by NAIP1 and NAIP2, respectively. Human NAIP detects both flagellin and T3SS components to assemble and activate the NLRC4 inflammasome. Basal transcription of NAIPs is regulated by interferon regulatory factor 8 (IRF8). NLRC4 enables ASC-dependent or ASC-independent CARD–CARD interaction for caspase 1 activation. **d** | Absent in melanoma 2 (AIM2) is activated by host-derived or pathogen-derived double-stranded DNA (dsDNA). During *Francisella tularensis* infection, IRF1 transcriptionally regulates the expression of guanylate-binding proteins (GBPs) and immunity-related GTPases (IRGs) to liberate bacterial dsDNA, which is recognized by AIM2. **e** | The pyrin inflammasome is activated when pyrin senses the modification of Rho induced by Rho-inactivating toxins. Activated caspase 1 or caspase 11 cleaves GSDMD within the linker between the amino-terminal and carboxy-terminal domains, thereby releasing the amino-terminal domain, which translocates to the plasma membrane and perforates the membranes to cause cell lysis (pyroptosis). The GSDMD pore may also serve as a conduit for releasing mature interleukin-1β (IL-1β) and IL-18. C, carboxy terminus; *F. novicida*, *Francisella tularensis* subsp. *novicida*; MCMV, murine cytomegalovirus; N, amino terminus; PYD, pyrin domain; *S.* Typhimurium, *Salmonella enterica* subsp. *enterica* serovar Typhimurium.

(TAK1) are shown to regulate NLRP3 activation[16–18] (FIG. 1b). In addition, Z-DNA-binding protein 1 regulates NLRP3 inflammasome activation during influenza A virus infection[19]. Owing to the broad nature of NLRP3 activation, it is unlikely that direct structural recognition or ligand binding is involved in its activation. NLRP3 may act as a sensor for homeostasis-altering molecular processes[20].

Pyrin. Activation of the most recently identified inflammasome, pyrin, depends on the inactivation of host small GTPases of the Rho family via Rho-modifying toxins, which inhibits the action of serine/threonine kinases PKN1 and PKN2 to relieve the phosphorylation of pyrin and promote its activation[21,22] (FIG. 1e). RhoA inactivation occurs in different residues, which can be sensed by pyrin, indicating that pyrin responds to perturbation of cytoplasmic homeostasis rather than directly recognizing a conserved PAMP and/or DAMP[20].

Ligand binding sensors

Caspase 11. Mouse caspase 11 or the human analogues, caspase 4 and caspase 5, directly bind to cytoplasmic lipopolysaccharide, which subsequently leads to non-canonical NLRP3 inflammasome activation[23] (FIG. 1b). The molecular events by which caspase 11 acquires protease function have been obscure. A recent report has shown that caspase 11 dimerization is sufficient for the autoprocessing that generates the fully active caspase 11 responsible for cleaving GSDMD[24]. Although it has been demonstrated that GSDMD is required for non-canonical NLRP3 inflammasome activation, the proximal events leading to inflammasome activation are not fully understood.

AIM2. The HIN domain of AIM2 binds to cytoplasmic double-stranded DNA (dsDNA) irrespective of the sequence of the dsDNA[25,26] (FIG. 1d). Binding of the sugar-phosphate backbone of dsDNA with the positively charged HIN-200 domain relieves PYD for self-oligomerization and its interaction with ASC for inflammasome activation.

NAIP–NLRC4. Recognition of bacterial ligands by NAIPs is an initial event in NLRC4 inflammasome activation. Human NAIP recognizes flagellin and components of the type 3 secretion system; mouse NAIP5 and NAIP6 bind directly to flagellin, and mouse NAIP1 and NAIP2 bind the needle and inner rod of the type 3 secretion system, respectively[27,28]. This ligand binding event is followed by NLRC4 recruitment and subsequent oligomerization for the assembly of a functional NAIP–NLRC4 inflammasome complex[29] (FIG. 1c). The production of NAIPs is under the control of interferon regulatory factor 8 (IRF8), which therefore is required for optimal NLRC4 inflammasome activation[30].

Promoting tumorigenesis

Although the primary role of inflammasome activation is to restrict pathogenic insults, persistent activation of inflammasomes propagates undesirable inflammatory responses[7]. It is well established that chronic inflammation contributes to most stages of tumorigenesis[31]. The pro-tumorigenic roles of inflammasome components have been mostly studied in tumour cell transplantation models and are centred on proliferation and survival, immunosuppression, angiogenesis and metastasis (FIG. 2).

Proliferation and survival

A common feature of all cancers is that they possess the ability to undergo increased proliferation and reduced cell death, both of which are stimulated by inflammation-driven mechanisms[31]. The inflammasome effector cytokines IL-1β and IL-18 released during acute and chronic inflammation may function in both a paracrine and an autocrine manner to induce cellular proliferation (FIG. 2a).

Notably, IL-18, but not IL-1β, produced from gastric epithelium promotes the development of gastric tumours in *gp130*$^{F/F}$ mice as a downstream effect of inflammasome activation. IL-18 inhibits caspase 8-mediated apoptosis in gastric cancer cells, thereby promoting cell survival in a cell-autonomous manner[32]. Furthermore, IL-18 production from immune cells in this particular study was not sufficient to drive gastric tumorigenesis, suggesting that IL-18 production from epithelial tumour cells rather than immune cells is detrimental. Perhaps IL-18 is produced in higher amounts from gastric epithelium, as the study showed higher gene expression of IL-18 in these cells than in immune cells. Although IL-1β does not have such a role in survival, it accelerates gastric tumorigenesis by a different mechanism, which is discussed in detail in the section on Immunosuppression[33]. Therefore, the functional dichotomy between IL-18 and IL-1β in gastric cancer could be explained, at least in part, by IL-18 acting on epithelial (tumour) cells expressing higher levels of IL-18 R to promote cell survival[32], whereas IL-1β-responsive immune cells provide a tumour-supporting microenvironment[33]. However, IL-1R signalling is important for proliferation of tumour cells in a spontaneous model of breast cancer[34]. IL-1β acts on breast cancer cells to enhance nuclear translocation of β-catenin, which results in induction of multiple oncogenes responsible for cell proliferation[35]. IL-18 production from gastric epithelial cancer cells is dependent on ASC, and ablation of ASC correlates with reduced NF-κB activation[32] (FIG. 2a). NF-κB being a mediator of ASC in the gastric epithelium is consistent with NF-κB promoting caecal carcinogenesis, in which ASC has been assigned a pro-tumorigenic role[36]. ASC suppresses IL-1R-mediated NF-κB signalling in primary melanoma cells to inhibit proliferation, whereas such a suppressive function is inert in metastatic melanoma cells. Instead, ASC contributes to an inflammasome-mediated positive feedback loop of IL-1R signalling in metastatic melanoma to promote proliferation[37].

Furthermore, studies have highlighted the role of individual inflammasome sensors in tumour proliferation and survival. NLRP3 activation in lymphoma cells produces IL-18, which attenuates dexamethasone-induced apoptosis, thereby promoting their survival (FIG. 2a). The decreased tumour growth of cutaneous squamous cell carcinoma (SCC) in the absence of AIM2 is associated

gp130$^{F/F}$ mice
A mouse model that is generated using a phenylalanine knock-in substitution at tyrosine 757 in the cytoplasmic domain of the interleukin-6 (IL-6) receptor β-chain (gp130). The mice rapidly develop tumours in the epithelium of the glandular stomach and highlight a key role for signal transducer and activator of transcription 3 (STAT3) signalling in gastric tumorigenesis.

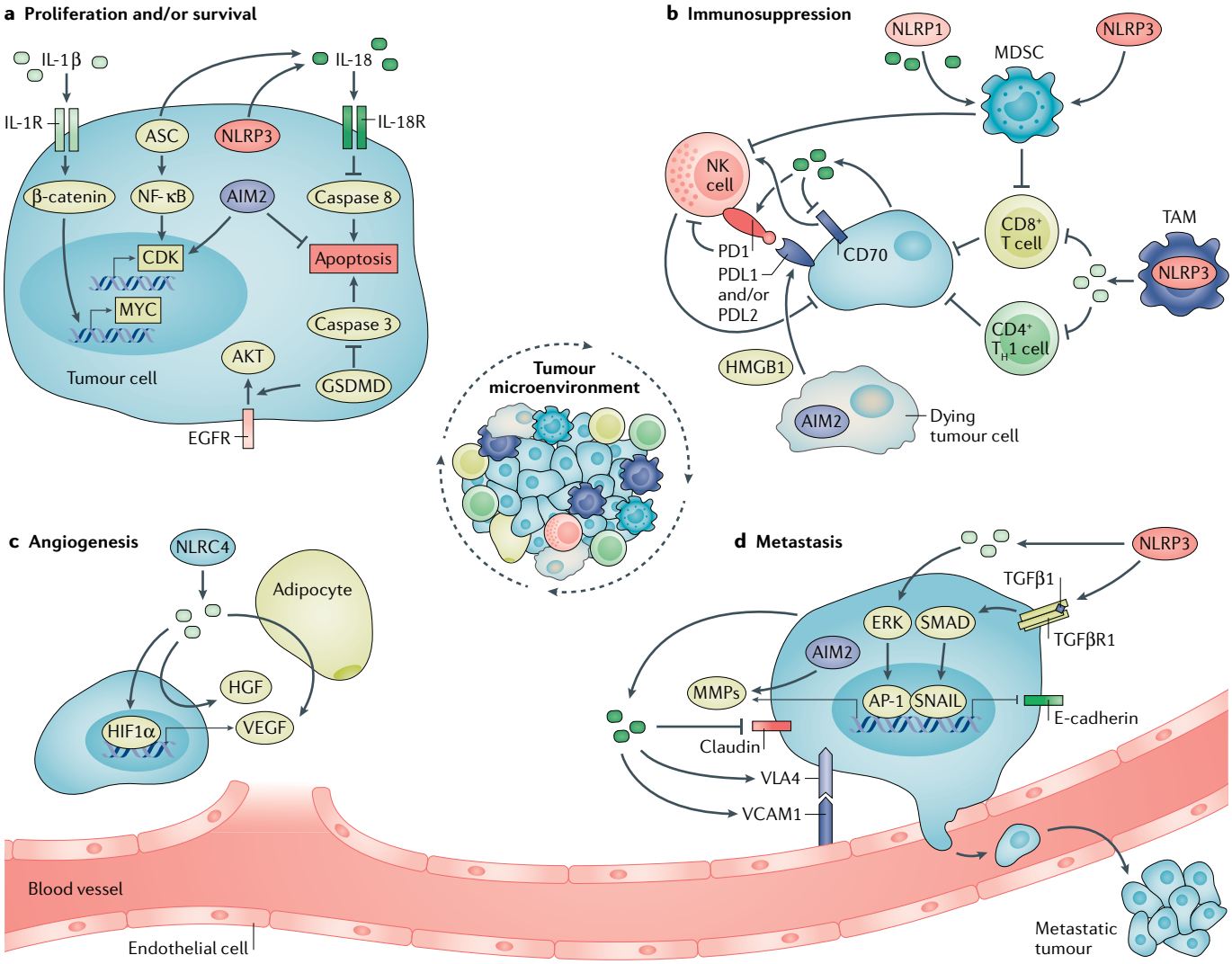

Fig. 2 | **Pro-tumorigenic roles of inflammasome components.** Inflammasome complexes are schematically depicted by labelled ovals. **a** | Proliferation and/or survival. Interleukin-18 (IL-18) produced from gastric cells inhibits caspase 8-mediated apoptosis in a cell-autonomous manner. NLRP3-mediated IL-18 production in lymphoma cells attenuates dexamethasone-induced apoptosis. IL-1β activates β-catenin, which induces MYC, which increases proliferation of lymphoma cells. Apoptosis-associated speck-like protein containing a CARD (caspase activation and recruitment domain) (ASC) in gastric epithelial cancer cells induces IL-18 production and NF-κB activation, which leads to cellular proliferation. Absent in melanoma 2 (AIM2) suppresses cell death and promotes cellular proliferation of cutaneous squamous cell carcinoma by inducing the expression of cyclin-dependent kinases (CDKs). Gasdermin D (GSDMD) inhibits caspase 3 activation to suppress apoptosis and promotes epidermal growth factor receptor (EGFR)-mediated protein kinase B and AKT signalling in non-small-cell lung cancer. **b** | Immunosuppression. NLRP1-mediated IL-18 production from both radio-resistant and radio-sensitive cellular compartments in multiple myeloma increases the generation of myeloid-derived suppressor cells (MDSCs) in the immune niche, which leads to tumorigenesis via inhibition of $CD8^+$ T cells and natural killer (NK) cells. NLRP3-mediated IL-1β in tumour-associated macrophages (TAMs) inhibits the antitumour immunity of $CD4^+$ T helper 1 (T_H1) cells and $CD8^+$ T cells. High mobility group box 1 (HMGB1) released from the disrupted mitochondrial iron metabolism in an AIM2-dependent manner promotes the upregulation of the immune checkpoint programmed cell death 1 ligand 1 (PDL1) in pancreatic ductal adenocarcinoma. IL-18 facilitates immune escape of gastric cancer cells by upregulating programmed cell death 1 (PD1) on NK cells and downregulating CD70 on tumour cells. CD70 increases the cytotoxicity of NK cells and induces tumour-specific T cell memory. **c** | Angiogenesis. NLRC4-mediated release of IL-1β acts on adipocytes to induce the production of vascular endothelial growth factor (VEGF). In tumour cells, IL-1β stimulates the secretion of hepatocyte growth factor (HGF) and induces hypoxia-inducible factor 1α (HIF1α) in tumour cells to transcriptionally regulate VEGF production. **d** | Metastasis. NLRP3 promotes epithelial-to-mesenchymal transition by enhancing transforming growth factor-β1 (TGFβ1)-mediated SMAD signalling, which downregulates E-cadherin in squamous cell carcinoma and gastric carcinoma. AIM2 increases the production and secretion of matrix metalloproteinases (MMPs) that promote the invasion of cutaneous squamous cell carcinoma. IL-1β increases the transcriptional activity of activator protein (AP-1), which induces MMPs, increasing the invasiveness of breast ductal cancer cells. IL-18 induces vascular cell adhesion molecule 1 (VCAM1) expression in hepatic sinusoidal endothelial cells (HSECs) and very late antigen 4 (VLA4) in melanoma cells, which facilitates VCAM1-dependent melanoma cell adhesion to HSECs.

Tumour microenvironment (TME). The cellular and molecular environment where tumour cells interact with infiltrating immune cells, fibroblasts, blood vessels and extracellular matrix.

Tumour-associated macrophages (TAMs). A class of mostly abundant immune cells present in the tumour microenvironment. They have a tumour-promoting phenotype via modulating tumour cell proliferation, tumour angiogenesis, invasion and metastasis.

Alarmins Damage-associated molecular patterns such as high mobility group box 1 (HMGB1) or interleukin-1α (IL-1α) released by damaged or necrotic cells.

Plasmacytoid dendritic cells (pDCs). A type I interferon-producing subset of dendritic cells with antigen-presenting potential.

with its ability to suppress cell death and promote cellular proliferation by inducing the expression of several genes involved in cell cycle regulation[38]. Although the precise regulatory mechanisms by which AIM2 induces these genes have not been reported, this might be due to the indirect effect of cytokines released by SCC cells in response to AIM2 inflammasome activation.

Another consequence of inflammasome activation besides cytokine maturation is GSDMD cleavage, which generates cytokine-releasing pores and culminates in pyroptosis[3]. The precise relevance and function of the pyroptosis executioner GSDMD in tumorigenesis are largely unknown. *Gsdmd*-silenced non-small-cell lung cancer cells exhibit reduced epidermal growth factor receptor (EGFR)–AKT signalling and enhanced caspase 3 cleavage and apoptosis, leading to suppression of tumour growth in transplanted mice[39]. Together, these studies show how inflammasome signalling provides proliferative and survival cues by activating NF-κB or β-catenin and inhibiting apoptosis during tumorigenesis. But how these diverse signals are distributed between and finally integrated in different cell types in distinct tumour settings requires further investigation.

Immunosuppression

In response to invading tumour cells, our immune system launches a potent antitumour response with an influx of inflammatory cells into the tumour microenvironment (TME)[40]. However, cancer cells can employ multiple mechanisms to evade immune surveillance. The release of the inflammasome-dependent cytokines IL-18 and IL-1β, and other co-stimulatory molecules (either directly from cancer cells or from neighbouring cells), is a well-known process for shaping an immunosuppressive TME during the progression of various cancers[33,41,42].

Myeloid-derived suppressor cells (MDSCs) are key components of the TME and are characterized by their ability to produce inhibitory cytokines and inducible nitric oxide synthase, to express arginase and to induce regulatory T (T_{reg}) cells, all of which collectively exert potent immunosuppressive activity[43]. IL-1β is instrumental in suppressing the tumour immune response by recruiting MDSCs. Xenograft tumours that overexpress IL-1β show a greater accumulation of immunosuppressive MDSCs and more rapid tumour progression[44], and *Il1r*$^{-/-}$ mice implanted with mammary carcinomas exhibit delayed accumulation of MDSCs and tumour growth[45]. The key role of IL-1β in MDSC recruitment and activation is also shown in gastric cancer. Here, overexpression of IL-1β leads to early recruitment of MDSCs during the spontaneous development of gastric adenocarcinoma, and IL-1β directly activates these MDSCs[33]. IL-18 suppresses the immune response through a distinct mechanism, which involves activation of T cell immune checkpoints. In particular, IL-18 promotes melanoma or colon carcinoma metastasis likely by inhibiting natural killer (NK) cell tumoricidal function through surface induction of the immunosuppressive co-stimulatory molecule programmed cell death 1 (PD1)[41] (FIG. 2b). IL-18 also facilitates the immune escape of gastric cancer cells by downregulating CD70, a co-stimulatory molecule that increases the cytotoxicity of NK cells and induces tumour-specific T cell memory[42]. Although these studies illustrate the direct immunosuppressive functions of IL-1β and IL-18, the specific inflammasome complexes that regulate these effectors are still being explored.

NLRP3 is crucial for the accumulation of MDSCs in tumours and the inhibition of antitumour T cell immunity after DC vaccination[46]. NLRP3 signalling in tumour-associated macrophages (TAMs) drives immunosuppressive CD4$^+$ T cell polarization in the TME of pancreatic ductal adenocarcinoma (PDA) via IL-1β[47]. In addition, NLRP3-dependent release of IL-1β causes immune cells, primarily CD4$^+$ T cells, to express and release IL-22, which has been associated with aggressive growth of multiple cancers including lung, breast, gastric and skin cancers[48]. In contrast to NLRP3, which mediates its effects by secreting inflammasome effector cytokines, studies point to AIM2 having a role in inflammasome-dependent release of alarmins that promotes tumorigenesis. Immunosuppressive tumour-associated plasmacytoid dendritic cells (pDCs) in lung cancer are associated with a heightened ability to secrete IL-1α that depends on AIM2 and subsequent calpain activation[49]. The mitophagy proteins PTEN-induced putative kinase 1 (PINK1) and parkin RBR E3 ubiquitin protein ligase (PARK2) suppress oncogenic KRAS-driven pancreatic tumorigenesis by keeping mitochondrial iron levels in check. Mechanistically, disrupted mitochondrial iron metabolism in the absence of these proteins induces AIM2-dependent high mobility group box 1 (HMGB1) release in PDA cells, which promotes upregulation of the immune checkpoint protein programmed cell death 1 ligand 1 (PDL1). Blocking HMGB1, but not IL-1β or IL-18, reduces neoplastic lesions and prolongs survival of the mice[50]. These two studies highlight the importance of understudied inflammasome-mediated alarmins in tumorigenesis. NLRP1 inflammasome-mediated IL-18 production in multiple myeloma augments the generation of MDSCs in the immune niche, leading to accelerated disease progression[51] (FIG. 2b). While the NLRP1 inflammasome is known to be activated by anthrax lethal toxin, *Toxoplasma* infection and haematopoietic stress[15], the mechanism of its activation in the TME is largely unknown. NLRP1 may sense haematopoietic stress or the disturbance of intracellular homeostasis in the TME of multiple myeloma. Overall, inflammasomes and their effector cytokines lead to the accumulation of MDSCs and expression of immune checkpoint molecules, thereby inhibiting tumoricidal function of T cells and NK cells.

Angiogenesis

Angiogenesis, the process by which new capillaries and vessels emerge from pre-existing vasculature, is vital for the progression from a small localized tumour to an enlarging tumour with the ability to metastasize. It is tightly regulated by numerous proangiogenic and antiangiogenic factors[52]. Inflammasome effector cytokines have been shown to regulate angiogenesis in several settings. Rapid tumour growth in mice implanted with IL-1β-expressing lung cancer cells is associated

with hyperneovascularization induced by proangiogenic factors secreted into the TME[53]. IL-1β produced from tumour cells induces the production of proangiogenic factors, such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor[53], and chemokines such as CXCL2. Moreover, IL-1β-mediated hypoxia-inducible factor 1α upregulation stimulates VEGF production in lung cancer cells[54] (FIG. 2c).

Although these studies exemplify the angiogenic functions of IL-1β, how distinct inflammasome complexes regulate this cytokine to modulate angiogenesis needs further investigation.

Metastasis

Tumour metastasis is a complex process that involves all sequential events from tumour cell dissemination from the primary foci to the formation of metastatic nodules in distant organs[55]. The environment of the distant metastatic target organs undergoes reprogramming, mostly by recruiting immune cells, to favour the growth of the tumour[55,56]. Tumour cell invasion and migration are key events in the metastatic cascade[56]. Several mechanisms are known for IL-1β-mediated or IL-18-mediated invasion and migration of cancer cells (FIG. 2d). These cytokines facilitate the invasion of malignant cells into the circulatory system and enhance the expression of adhesion molecules on endothelial and malignant cells, allowing dissemination and implantation into remote tissues[57]. *Il1b*$^{-/-}$ mice have reduced lung metastasis and increased survival following inoculation of B16 melanoma cells[58]. Similarly, systemic administration of IL-1 R antagonist (IL-1RA) reduces the size and numbers of hepatic metastases of melanoma and improves survival of the mice[59]. *Il1b*$^{-/-}$ mice are comparatively less resistant to hepatic metastasis than *Casp1*$^{-/-}$*Casp11*$^{-/-}$ mice, which fail to produce both mature IL-1β and IL-18, suggesting that both cytokines contribute to metastasis. In this particular model, IL-18 acts downstream of IL-1β to facilitate inflammation-augmented hepatic metastasis by increasing vascular cell adhesion molecule 1 (VCAM1) expression in hepatic sinusoidal endothelial cells (HSECs), which allows cancer cell adhesion[57]. IL-18 also induces very late antigen 4 in melanoma cells[60], which facilitates VCAM1-dependent melanoma cell adhesion to HSECs[61]. Depletion of IL-18 in transplanted melanoma cells or systemic neutralization of IL-18 in recipient mice reduces lung metastasis[41], indicating that IL-18 from cancer cells also contributes to metastasis. The outcome of metastasis appears to be greatly affected by the cancer cell type and source of IL-18 production. For instance, IL-18 promotes melanoma[57] but suppresses colon cancer metastasis to the liver[62]. Colon carcinoma-induced IL-18 production from liver Kupffer cells promotes FAS–FAS ligand (FASL)-driven cell death[62] (FIG. 3). It is interesting to note that despite using the same intrasplenic injection model, these two studies showed contrasting outcomes of hepatic metastasis, indicating that IL-18 production induced by different cancer cell types dictates metastasis.

Similarly, the effect of NLRP3 activation may differ according to the cancer type, route of inoculation and metastatic site. Hepatic metastasis following splenic injection of colon cancer cells is increased in *Casp1*$^{-/-}$*Casp11*$^{-/-}$ mice and *Nlrp3*$^{-/-}$ mice, which is dependent on IL-18 but not IL-1β[62]. In contrast, a similar study has suggested that NLRP3-dependent IL-1β secretion from macrophages may shift tumour cells to a more migratory phenotype to drive hepatic dissemination and metastasis of colon cancer in mice[63]. However, a critical flaw in the latter study is that different strains of wild-type and knockout mice have been used, which generates difficulty in assessing the contribution of the gene of interest. On the other hand, the reduced lung metastasis in *Casp1*$^{-/-}$ and *Nlrp3*$^{-/-}$ mice after orthotopic implantation or intravenous injection of E0771 breast cancer cells supports the idea that inflammasome activation regulated by NLRP3 encourages metastasis in this setting[64]. Furthermore, there is evidence that NLRP3 also promotes metastasis independently of its inflammasome activity. *Nlrp3*$^{-/-}$ mice, but not *Casp1*$^{-/-}$ mice, have lower numbers of lung metastases after intravenous inoculation of melanoma or prostate carcinoma cells. Resistance to metastasis is attributed to enhanced NK cell activity in the *Nlrp3*$^{-/-}$ mice[65]. Although tumour growth and lung metastasis in *Casp1*$^{-/-}$*Casp11*$^{-/-}$ mice are comparable to those in wild-type mice in a model of breast cancer with spontaneous metastasis (PyMT-MMTV transgenic mice)[34], lung metastasis is reduced in *Nlrp3*$^{-/-}$ mice implanted with tumours derived from PyMT-MMTV transgenic mice[64]. Further study is required to explain whether this discrepancy results from inflammasome-independent functions of NLRP3 or from the differential contribution of inflammasomes in tumour cells versus host cells.

Tumour cells lose epithelial markers and gain mesenchymal traits during primary tumour invasion and metastasis[66]. IL-1β and IL-18 have been reported to induce epithelial-to-mesenchymal transition (EMT) in multiple cell types[67]. IL-1β downregulates E-cadherin expression and upregulates SNAIL (also known as SNAI1) expression in SCC[68,69] and gastric cancer cells[70]. Tumour invasion also involves degradation of the extracellular matrix by matrix metalloproteinases (MMPs)[71]. IL-1β synergistically acts with growth factors to upregulate MMP9 by increasing transcriptional activity of activator protein (AP-1), thereby increasing the invasiveness of breast ductal cancer cells[72]. Furthermore, interruption of cell–cell adhesion is a crucial step in invasion and metastasis. IL-18 enhances breast cancer cell migration via downregulation of claudins, which are junctional adhesion molecules[73]. Of interest, NLRP3 can promote EMT by enhancing TGFβ1 signalling and SMAD activation independently of caspase 1 or inflammasome-regulated cytokines[74,75], and reduced invasion of cutaneous SCC in the absence of AIM2 is associated with decreased production of MMP13 and MMP1 (REF.[39]).

Together, these studies show that the role of inflammasomes in metastasis is bidirectional and that the outcomes vary depending on factors such as the type of cancer and the route of inoculation. Extending our knowledge gained from transplantable tumours, it would be exciting to explore how inflammasomes are involved in metastasis from primary tumour settings.

Hepatic sinusoidal endothelial cells
(HSECs). A special type of endothelial cells that represent the interface between blood cells on the one side and hepatocytes and hepatic stellate cells on the other side.

Epithelial-to-mesenchymal transition
(EMT). A process by which epithelial cells lose their polarity and cell–cell adhesion properties and acquire mesenchymal fibroblast-like properties.

Matrix metalloproteinases
(MMPs.) A family of endopeptidases capable of degrading extracellular matrix components, influencing multiple cellular processes such as migration and adhesion.

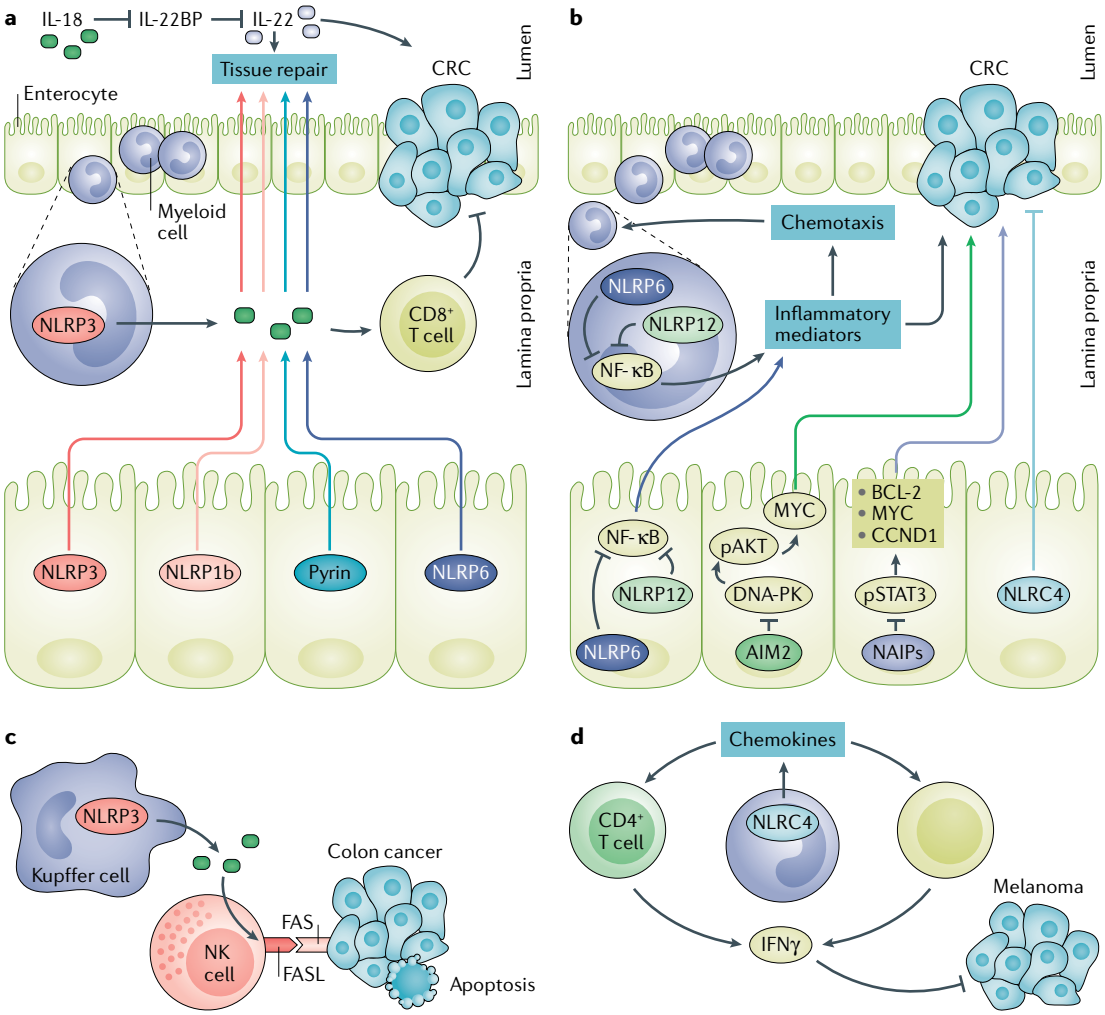

Fig. 3 | **Protective roles of inflammasomes in cancer. a** | NLRP3, NLRP1b, pyrin and NLRP6 inflammasomes (depicted by labelled ovals) mediate the production of interleukin-18 (IL-18), which enhances the barrier function and regenerates epithelial cells to protect against colorectal cancer (CRC). IL-18 modulates the bioavailability of IL-22, which has dual effects in CRC. Pyrin-mediated release of IL-18 promotes $CD8^+$ T cells to inhibit CRC. **b** | NLRP6 and NLRP12 function in both the myeloid cells and enterocytes to negatively regulate the NF-κB-mediated expression of inflammatory cytokines and chemokines. These inflammatory mediators induce the chemotaxis of immune cells into the lamina propria during colitis. Absent in melanoma 2 (AIM2) inhibits DNA-dependent protein kinase (DNA-PK)-mediated phosphorylation of AKT and MYC induction to inhibit overt proliferation of intestinal stem cells. NLR family apoptosis inhibitory proteins (NAIPs) inhibit signal transducer and activator of transcription 3 (STAT3) hyperactivation and cellular proliferation to prevent CRC, whereas NLRC4 restricts proliferation and drives apoptosis of epithelial cells. **c** | IL-18 released from Kupffer cells in an NLRP3 inflammasome-dependent manner controls liver metastasis of colon carcinoma by enhancing FAS ligand (FASL) expression on natural killer (NK) cells, promoting their tumoricidal function. **d** | NLRC4 in myeloid cells releases chemokines that potentiate the production of interferon-γ (IFNγ) from $CD4^+$ and $CD8^+$ T cells to suppress melanoma growth. Cytokine-dependent roles of inflammasomes are presented in parts **a** and **c**. Cytokine-independent roles of inflammasomes are presented in parts **b** and **d**. IL-22BP, IL-22 binding protein; pAKT, phosphorylated AKT; pSTAT3, phosphorylated STAT3.

Suppressing tumorigenesis

The tumour-suppressive function of the inflammasome has been mostly demonstrated in the colorectal cancer (CRC) model (FIG. 3). Mice lacking the inflammasome-initiating sensors NLRP1b[76], NLRP3 (REFS[77,78]), AIM2 (REFS[79,80]), NLRC4 (REFS[81,82]) and pyrin[83] are hypersusceptible to colitis-associated cancer induced by the DNA-damaging agent azoxymethane (AOM) and the chemical colitogen dextran sulfate sodium (DSS). AOM is a precursor of methylazoxymethanol, which can damage DNA by methylation of guanine. Tumours induced by AOM frequently carry mutations in KRAS and β-catenin, mimicking human CRC. AOM combined with DSS accelerates tumour development and is commonly used to study inflammation-mediated CRC[84]. Inflammasome sensors assemble a fully functional inflammasome complex by recruiting ASC and caspase 1, which are also important in mediating protection against CRC[76–79,81,82] (TABLE 1).

Azoxymethane
(AOM). A potent carcinogen that is used to induce colon carcinoma in mice and rats. It is metabolized to methylazoxymethanol in the liver and then reaches the colon via the bloodstream rather than the bile.

Protection in colorectal cancer

The ability of NLRP1b, NLRP3 and pyrin to protect against CRC is attributed to the effector function of caspase 1 to mediate secretion of IL-18, a key cytokine that promotes epithelial barrier regeneration during the

early stages of colitis[77,78,85–88] (FIG. 3a). In addition, the ability of IL-18 to mount NK cell-mediated or T cell-mediated antitumour immune responses may contribute to this protection[89]. Injection of recombinant IL-18 into *Casp1*$^{-/-}$ mice reduces the prevalence of tumours in response to AOM and DSS[78]. By contrast, another study found that mice with conditional deletion of IL-18 in either epithelial cells or haematopoietic cells are more resistant to DSS-induced colitis[90]. Furthermore, amelioration of intestinal inflammation by neutralization of IL-18 suggests a detrimental role of IL-18 in colitis[91,92]. Notably, IL-18 can inhibit the expression of soluble IL-22 binding protein in haematopoietic cells, which modulates the bioavailability of IL-22, a cytokine that suppresses early intestinal damage but also promotes tumorigenesis over time[93] (FIG. 3a). Therefore, early local production of IL-18 by enterocytes or cells residing in the lamina propria may contribute to epithelial repair after injury, whereas its excessive production during chronic inflammation potentially promotes tumorigenesis.

Signalling through the NLRP3 inflammasome in the haematopoietic[77] and non-haematopoietic compartment[85] is essential for mediating protection against colonic tumorigenesis. One study has suggested that *Nlrp3*$^{-/-}$ mice are more resistant to DSS-induced colitis than are wild-type mice[94], whereas another study has found similar tumour prevalence between wild-type mice and *Nlrp3*$^{-/-}$ mice[81]. However, colorectal tumorigenesis induced by AOM in the presence of a high-cholesterol diet is mediated by NLRP3 inflammasome activation[95]. Could these contrasting roles be explained to a certain extent by the differences in the gut microbiota between different animal facilities or the use of littermate versus non-littermate controls? It is important to note that genetically modified mice carrying the gain-of-function mutation *Nlrp3*^{R258W}, which is homologous to the human *NLRP3*^{R260W} mutation, are strongly resistant to experimental colitis and CRC. In these mice, enhanced IL-1β production in the colon reshapes the intestinal microbiota, which in turn supports the development of T_{reg} cells to restrict gut inflammation[96]. Furthermore, increased production of IL-1β by ASC-dependent inflammasome activation in the absence of PTPN2 in myeloid cells protects against CRC. In this particular model, increased colitis in the mice lacking PTPN2 is associated with decreased tumorigenesis[97]. Injection of recombinant IL-1β into *Nlrp1b*$^{-/-}$ mice mediates protection against colitis[76]. This suggests that IL-1β plays an important role in inflammasome-mediated protection against colitis. By contrast, a previous study has shown that *Il1r*$^{-/-}$ mice have susceptibility to CRC that is similar to that of wild-type mice[87], which might be due to a nullified outcome of differential IL-1R signalling in different tissues. Indeed, a recent study has elegantly demonstrated opposing roles of cell type-specific IL-1R signalling in CRC. The pro-tumorigenic roles of IL-1R in epithelial and T cells are counteracted by its effects on myeloid cells, particularly neutrophils, in which IL-1R signalling contributes to deterring tumour-infiltrating bacteria and dampening CRC-promoting inflammation[98]. Similarly, in skin tumorigenesis, inflammasome activation driven by ASC in myeloid cells favours epithelial skin tumorigenesis, whereas ASC in keratinocytes serves to limit proliferation, possibly through p53 activation in an inflammasome-independent manner[99]. Thus, inflammasome signalling elicits cell type-specific responses, which altogether determine the propensity for tumorigenesis.

Cytokine-independent protection by inflammasomes in colorectal cancer. The ability of inflammasome sensors to provide protection against cancer does not always rely on the effector cytokines. The protective role of NLRC4 in the development of CRC is associated with its intrinsic ability to restrict the proliferation and drive the apoptosis of epithelial cells in both steady state and the early phase of tumorigenesis[81] (FIG. 3b). In addition to its role in CRC, NLRC4 amplifies inflammatory signalling pathways in macrophages independently of inflammasome assembly and potentiates the production of IFNγ in $CD4^+$ and $CD8^+$ T cells to suppress melanoma growth in mice[100] (FIG. 3d). Although mouse NAIP1–NAIP6 are components of the NLRC4 inflammasome, NAIP-mediated protection against CRC is related to the ability of NAIPs to inhibit hyperactivation of the transcription factor signal transducer and activator of transcription 3 (STAT3) and the expression of genes encoding anti-apoptotic and proliferation-related molecules, which are NLRC4 inflammasome-independent and epithelium-intrinsic functions of NAIPs[101] (FIG. 3b). Furthermore, simultaneous recognition of flagellin in tumour cell lines by NAIPs and TLR5 induces tumour cell clearance by innate immune cells and activation of tumour-specific T cell responses in mice[102].

An inflammasome-autonomous function of AIM2 in inhibiting inflammation-induced and spontaneous colorectal tumorigenesis has been suggested by two independent studies[79,80]. AIM2 interacts with DNA-dependent protein kinase to limit PI3K–AKT activation[79,103], thereby suppressing overt proliferation of colonic stem cells and inducing cell death[80,103] (FIG. 3b). A similar negative regulatory effect of the putative inflammasome sensor NLRC3 on PI3K–AKT signalling in limiting mTOR activation has been described to inhibit cellular proliferation[104]. Although the specific ligand that AIM2 senses in the colon has yet to be determined, host DNA released after intestinal injury or DNA derived from the gut microbiota might activate AIM2 (REF.[105]). Indeed, AIM2 localizes to DNA in the nucleus of intestinal epithelial cells and bone marrow cells in response to dsDNA breaks caused by ionizing radiation or chemotherapeutic agents[106]. Whether the DNA-sensing property of AIM2 is required for its tumour-suppressive function is not known. Another mechanism by which AIM2 restricts tumorigenesis is through antagonizing NF-κB activity to induce apoptosis, as shown in breast cancer cells[107,108].

NLRP6 (REFS[109–111]) and NLRP12 (REF.[112]) are potential inflammasome sensors. NLRP6-dependent secretion of mucin 2 (MUC2) in the intestinal epithelium (FIG. 4) is required to clear colitogenic bacteria. However, MUC2 secretion can be either dependent or independent of the inflammasome[110,113]. Likewise, despite of its

Mucin 2
(MUC2). A glycoprotein that is particularly prominent in the gut and is secreted from goblet cells in the epithelial lining into the lumen of the large intestine.

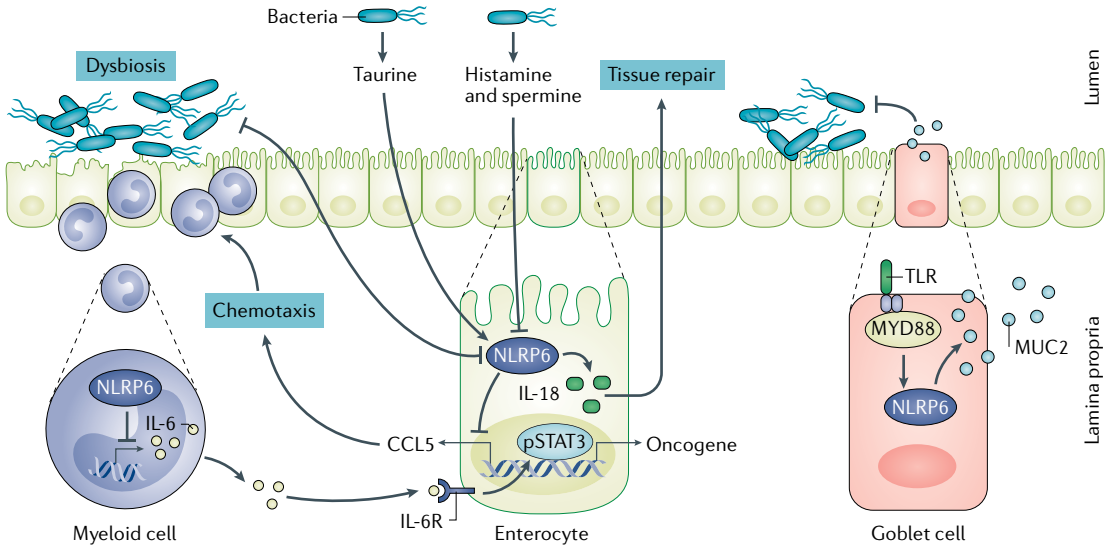

Fig. 4 | **Inflammasome–microbiota axis in intestinal homeostasis.** Several immune mechanisms work in concert with the intestinal microbiota to maintain intestinal homeostasis and provide protection against colorectal cancer (CRC). Inflammasome complexes are schematically depicted by labelled ovals. Dysbiosis inhibits NLRP6 inflammasome activation in enterocytes. Conversely, NLRP6 in enterocytes inhibits intestinal dysbiosis and CCL5-mediated recruitment of immune cells into the lamina propria. Increased interleukin-6 (IL-6) production from myeloid cells in the absence of NLRP6 acts on neighbouring enterocytes to activate the oncogenic transcription factor signal transducer and activator of transcription 3 (STAT3). The microbial metabolite taurine activates, whereas histamine and spermine suppress, NLRP6-mediated IL-18 secretion. NLRP6 in sentinel goblet cells induces the secretion of mucin 2 (MUC2), which expels intruding bacteria found in the inner mucous layer, providing protection against CRC. pSTAT3, phosphorylated STAT3.

ability to form inflammasomes, the protective function of NLRP12 against colitis and associated tumorigenesis is attributed to the negative regulation of inflammation via suppression of NF-κB pathways[114,115] (FIG. 3b).

Inflammasome–microbiota–diet axis

The composition of symbiotic microorganisms that live in our gut, the so-called gut microbiome, is one of the principal environmental factors that contributes to immune homeostasis in the intestine[116]. Disturbance of the microbial ecology results in the development and progression of CRC, which can be modulated by the use of broad-spectrum antibiotics[117]. In addition to their conventional role as guardians of cellular integrity, inflammasomes can serve as surveillance systems, regulating the host–microbiota crosstalk in health and disease. The contrasting phenotypic outcomes in mice with identical genetic deficiencies are intriguing and can largely be attributed to different microbial compositions across mice. The notion of inflammasomes regulating the gut microbial landscape emerged from a study that found that a 'colitogenic' gut microbial community, defined by an increased or decreased relative abundance of Prevotellaceae or *Lactobacillus*, respectively, predisposes *Nlrp6*$^{-/-}$ mice to exacerbated DSS-induced colitis and tumorigenesis or low-grade intestinal inflammation[109]. Dysbiosis has also been reported in mice that are deficient in the inflammasome components AIM2, NLRP3, ASC, caspase 1 and IL-18 (REFS[109,118,119]). The distinct microbiota profile characterized by an increased relative abundance of *Lactobacillus murinus* and decreased abundance of colitogenic bacteria, such as *Akkermansia muciniphila*, is associated with decreased gut inflammation and CRC in *Nlrp3*^{R258W} mice[96]. The colitogenic gut microbiota can be transmissible, as suggested by the altered susceptibility of mice lacking NLRP6, AIM2 or NLRP12 following reciprocal exchange of gut microbiota with wild-type mice[105,109,120]. Dysbiosis driven by NLRP6 deficiency elevates the production of CCL5, a chemokine that recruits immune cells in the intestinal lamina propria and mediates the secretion of IL-6, which in turn acts on epithelial cells to drive a pro-tumorigenic response[82] (FIG. 4). Consistently, CCL5 deficiency prevents dysbiosis-induced colitis and tumorigenesis, suggesting that CCL5 mediates immune dysregulation downstream of the microbial community[82,109]. Furthermore, metabolites produced by the gut microbiota may influence inflammasome-mediated disease outcomes. The microbiota-derived metabolite taurine promotes the production of IL-18 in an NLRP6-dependent manner, whereas histamine and spermine inhibit NLRP6 (REF.[121]) (FIG. 4). An additional mechanism that NLRP6 employs to protect against tumorigenesis is to induce the secretion of MUC2 in sentinel goblet cells, which expels intruding bacteria from the inner mucous layer[110,113] (FIG. 4). This phenotype is unaffected by microbiota transfer, highlighting that certain biological functions of NLRP6 are not influenced by the gut microbiota.

The effects of the inflammasome–gut microbiota axis have been extended from the gut to systemic metabolic and inflammatory processes. The microbiota composition influences the susceptibility of mice lacking NLRP3 to non-alcoholic steatohepatitis, which can progress to hepatocellular carcinoma (HCC)[122]. However, more recent studies argue that dysbiosis observed in inflammasome-deficient mice is dependent on the

Nlrp3^{R258W} mice
Genetically modified mice carrying the R258W mutation in the *Nlrp3* gene, which corresponds to the R260W mutation in the *NLRP3* gene in humans. These mice develop severe cutaneous lesions, including erythema, scaling and thickening of both the epidermis and the dermis, symptoms that recapitulate urticaria-like skin lesions reported in patients with Muckle–Wells syndrome.

facilities used to house the animals[123,124]. Diet and the aseptic techniques used by different facilities may affect the ecology of the gut microbiota, which in turn affects the activation status of inflammasomes. Indeed, mice fed with a high-fat diet (HFD) have different microbial communities from those fed a normal diet or a low-fat diet[125]. Dietary cholesterol and dietary-derived deoxycholic acid serve as endogenous danger signals that activate the NLRP3 inflammasome and contribute to HFD-related colonic inflammation and CRC[95,126]. On the other hand, NLRP3 activation by short-chain fatty acids or inhibition by omega-3 fatty acids prevents inflammation[127,128]. Lastly, obesity is a risk factor in numerous cancers, and recent evidence presents inflammasome involvement as one link between this form of metabolic dysregulation and tumour-sustaining angiogenesis. Tumorigenesis in HFD-fed mice following orthotopic implantation of breast cancer cells is mediated by NLRC4 inflammasome activation. There is increased gene expression of *NLRC4* in the TME of obese humans and mice. Immune cells with pronounced NLRC4 inflammasome activation are recruited to the TME of obese mice, leading to IL-1β release, which acts on adipocytes to promote VEGF production[129]. Metabolites of an HFD or the alteration of the gut microbiota in HFD-fed mice may activate the NLRC4 inflammasome[121,125]. These studies highlight a dynamic and emerging association between diet, the microbiota and inflammasome activation, indicating that dysbiosis influenced by inflammasomes should be revisited and interpreted with care.

Inflammasomes in human cancer

Evidence presented above from studies of murine models highlights the multifaceted roles of inflammasomes in cancer. Inflammasome signalling in human cancer is controlled by a combination of genetic factors, such as inherited genomic variations and acquired somatic mutations, and environmental factors that can affect epigenetics and gene expression and ultimately provide stimulation for activation. Our understanding of the importance of inflammasomes in human cancer susceptibility has been enhanced by investigations of the genotype–phenotype correlations and gene expression profiling in cancers.

Gene polymorphisms and mutations

Polymorphisms in the genes encoding inflammasome components are associated with increased predisposition to multiple cancers. Several single-nucleotide polymorphisms (SNPs) in the *NLRP3* region are associated with susceptibility to Crohn's disease[130,131], which is a strong risk factor for CRC. Among those SNPs, the gain-of-function *NLRP3*^{Q705K} variant is associated with poorer survival in advanced-stage CRC[132]. The same *NLRP3* variant is a risk allele for melanoma in Swedish males[133]. Individuals with polymorphisms in *NLRP3*, *NLRP12* and *CASP1* have a greater risk of gastric cancer when they are infected with *Helicobacter pylori*, highlighting the interplay between genetic and environmental factors in tumorigenesis[134]. A hyperactive *NLRP1* mutation causes spontaneous skin inflammation and a predisposition to skin cancer[135]. However, other reports on the association of *NLRP1* polymorphisms with asbestos-associated mesothelioma[136,137] are controversial. The *AIM2* gene contains a site for microsatellite instability that results in frequent gene mutation in CRC and small bowel cancers[138,139]. In addition, *AIM2* is a potential oncogenic driver in endometrial cancer, though most microsatellite-containing genes are bystander genes[140]. Altogether, SNP associations provide clues for determining which inflammasome components are important for the pathogenesis of specific cancer types. Going further, it would be helpful to examine the functional outcome of individual SNPs, such as alterations in inflammasome function or changes in expression levels.

Although inflammation is associated with a higher risk of cancer, it might be protective in some cases. Patients with familial Mediterranean fever (FMF) suffer from autoinflammation owing to a hyperactive pyrin inflammasome; however, they have a lower combined incidence of cancer than the general population[141]. It could be that pyrin inflammasome activation is beneficial in inhibiting tumorigenesis, but these results should be interpreted with caution, as the drugs used to treat patients with FMF have antitumour effects. Further studies are needed to define the relationship between genetic polymorphisms in inflammasomes and general cancer incidence or susceptibility to certain cancers.

Differential expression

Gene expression profiling in many cancers has revealed differential gene expression of inflammasomes, which implies that inflammasome signalling is altered in cancer. In certain types of cancer, expression of inflammasome components is upregulated. Components of the NLRP3 and AIM2 inflammasomes are highly expressed in nasopharyngeal and lung cancer tissues compared with normal tissue, and this molecular signature is correlated with improved probability of survival in nasopharyngeal cancer[142,143]. On the other hand, the NLRP3 inflammasome is overexpressed in oral SCC tissue and is associated with unfavourable pathology. In oral SCC tissue, enhanced expression of ASC is an independent predictor of poor prognosis[144]. The discrepancy in the role of NLRP3 in cancer of anatomically adjacent oral and nasopharyngeal epithelia could be due to the distinct aetiology of cancers in these tissues. While oral SCC is more attributed to chronic exposure of carcinogens such as tobacco, nasopharyngeal carcinoma is strongly linked with Epstein–Barr virus infection. Therefore, it would be interesting to check whether inflammasomes have a protective role in other virus-associated cancers. The NLRP3 inflammasome is associated with the development of lymphoproliferative malignancy secondary to Sjögren syndrome. Patients who later develop non-Hodgkin lymphoma express higher levels of NLRP3 inflammasome at the time of diagnosis[145]. Inflammasome activity also has a crucial role in drug resistance in acute lymphoblastic leukaemia. Owing to hypomethylation, *CASP1* and *NLRP3* expression is higher in glucocorticoid-resistant cells and cells at relapse. In vitro inhibition of caspase 1 blocks glucocorticoid receptor cleavage, thereby restoring sensitivity to treatment[146]. *NLRP3* and *NAIP* expression

Deoxycholic acid
A bile acid that emulsifies and solubilizes dietary fats in the intestine.

Crohn's disease
An inflammatory bowel disease that involves chronic inflammation of the digestive tract.

Familial Mediterranean fever
(FMF). Mutations in the gene encoding pyrin (*MEFV*) are associated with FMF, which is an autosomal recessive, autoinflammatory disorder characterized by episodic fever and neutrophil-mediated inflammation of serosal tissues.

Sjögren syndrome
An autoimmune disease that mostly affects the salivary and lacrimal glands, resulting in dry mouth and dry eyes.

is increased in urine sediments of patients diagnosed with bladder cancer. A combination of NAIP and the established marker CK20 results in greater sensitivity for predicting the histological outcome of bladder cancer, suggesting that inflammasome genes could be useful as non-invasive diagnostic tools for bladder cancer[147]. In addition, NLRP12 is highly expressed in prostate cancer epithelium compared with adjacent benign tissues. Despite high expression of pro-IL-1β and pro-IL-18, mature IL-1β and IL-18 are not detected in malignant prostate cancer cells, implying that NLRP12 may promote progression of prostate cancer independently of inflammasome activity[148].

Reduced expression of inflammasome components in certain tumours may be indicative of their tumour suppressor function. For instance, the histone methyltransferase G9A mediates invasion and migration of lung cancer cells by repressing *CASP1* expression. *CASP1* is downregulated in lung adenocarcinoma compared with normal tissue, and reduced *CASP1* expression is associated with poor survival, indicating that *CASP1* may serve as a prognostic marker in lung cancer[149]. The level of *AIM2* expression is lower in CRC tumours than in adjacent normal tissue. The lack of *AIM2* expression is correlated with higher tumour grade and is associated with poorer survival[150]. This finding is supported by gene expression analysis from The Cancer Genome Atlas database showing lower levels of *NLRP1*, *NLRP3*, *NLRC4* and *AIM2* expression in CRC than in healthy controls, but results vary when different databases are used for the analysis[151]. Evaluation of inflammasome expression in HCC reveals a dynamic pattern during the progression of the disease: the NLRP3 and AIM2 inflammasomes are upregulated in cirrhotic tissue but then are lost in cancer. Moreover, lower expression of these inflammasome components correlates with advanced clinicopathological features of HCC. These results are not straightforward but may provide insight into how chronic inflammation fosters malignant transformation. Cells proliferating in the presence of persistent inflammation and inflammasome activation may accumulate mutations and lose expression of tumour-suppressive NLRP3, ultimately leading to cancer progression[152]. Although not well studied as an inflammasome sensor, NLRC5 is a key transcriptional co-activator of MHC class I genes. Reduced NLRC5 expression is associated with impaired $CD8^+$ T cell activation and immune evasion in cancers. Lower NLRC5 expression correlates with reduced survival in melanoma and in bladder and cervical cancers, suggesting that NLRC5 may be used as a prognostic marker for multiple cancers[153].

Therapeutic approaches

Therapeutics targeting inflammasome activity have been shown to be effective for autoinflammatory periodic fever syndromes and have been used experimentally for treating inflammation-driven neurodegenerative diseases and metabolic disorders. Although there is ample evidence that inappropriate inflammasome regulation contributes to the pathogenesis of human cancers, where and how inflammasome therapy is applicable in cancer should be evaluated critically. One emerging approach could be modulating inflammasome activation while administering chemotherapeutics or cell therapeutics to maximize their efficacy. Prospectively, cytokine blockade may be useful in various clinical settings, ranging from preventive regimens for individuals predisposed with chronic inflammation, to therapeutic intervention to restrict tumour progression in precancerous settings and to palliative or adjuvant treatment for advanced cancers.

Inflammasome signalling during therapy

Recent findings address the interactions between chemotherapeutic agents and inflammasome activation. Cancer chemotherapeutics, such as anthracyclines and platinum-based drugs, elicit cytotoxicity against malignant cells. This is achieved in part by inducing immunogenic cell death, which can be modulated by inflammasome signalling[154]. The observation that caspase activity augments antitumour immune responses induced by anthracyclin[155] led to the discovery that NLRP3 inflammasome activation is required for effective cancer chemotherapy[156]. The release of various DAMPs, including ATP, HMGB1 and IL-1α, from dying tumour cells activates the NLRP3 inflammasome in DCs to release IL-1β, which is crucial for priming IFNγ-producing $CD8^+$ T cells and activating NK cells[156] (FIG. 5). Furthermore, a loss-of-function polymorphism in the purinergic receptor P2RX7 (also known as P2X7) in patients with breast cancer who were treated with anthracyclines has been correlated with increased metastasis[156]. On the other hand, gemcitabine and 5-fluorouracil (5-FU) activate the NLRP3 inflammasome via cathepsin B release in MDSCs, thereby producing IL-1β levels insufficient for $CD8^+$ T cell priming but sufficient to drive IL-17-producing $CD4^+$ T cells[157] (FIG. 5). Likewise, the NLRP3 inflammasome mediates resistance to 5-FU treatment for oral SCC[158] and reduces the efficacy of DC-derived antitumour vaccines against grafted tumour cells[46].

A recent study showed that AIM2 inflammasome activation by antibody-dependent cellular phagocytosis of tumour DNA into macrophages following monoclonal antibody-based cancer treatment suppresses antitumour immunity by upregulating PDL1 and indoleamine 2,3-dioxygenase[159]. This finding suggests that the use of immune checkpoint blockade in combination with antibody treatment may be beneficial to boost treatment efficacy (FIG. 5).

Although IL-1β signalling enhances the efficacy of doxorubicin against breast adenocarcinomas and fibrosarcomas[160], the efficacy of cisplatin against malignant mesothelioma tumour cells is increased by concomitant use of IL-1RA[161]. In addition, impaired doxorubicin efficacy towards breast cancer cells in the presence of IL-18 suggests a role of IL-18 in the development of chemotherapy resistance[162]. Eradicating large solid tumours at advanced stages remains challenging, and new attempts have been made to harness inflammasome signalling for better treatments. Adoptive therapy with chimeric antigen receptor-redirected T cells engineered with inducible IL-18 release mounts acute inflammation

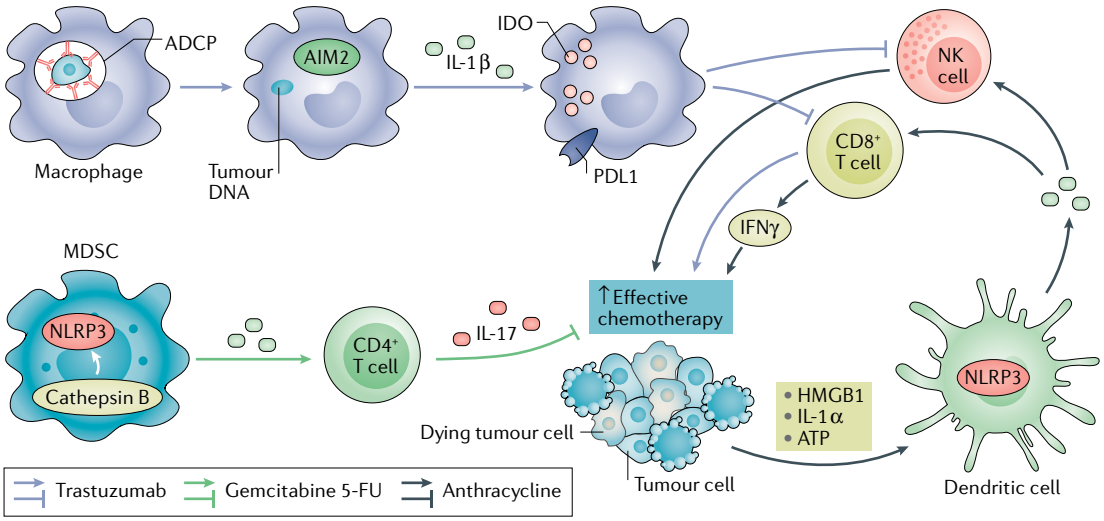

Fig. 5 | **Inflammasome signalling during chemotherapy.** Gemcitabine and 5-fluorouracil (5-FU) activate the NLRP3 inflammasome (inflammasome complex schematically depicted by ovals) in myeloid-derived suppressor cells (MDSCs) to produce interleukin-1β (IL-1β), which primes $CD4^+$ T cells to release IL-17. High mobility group box 1 (HMGB1), IL-1α and ATP released from dying tumour cells activate the NLRP3 inflammasome in dendritic cells to release IL-1β, which is crucial for activating natural killer (NK) cells and priming $CD8^+$ T cells to produce interferon-γ (IFNγ). Antibody-dependent cellular phagocytosis (ADCP) of tumour cells by macrophages leads to absent in melanoma 2 (AIM2) inflammasome activation. IL-1β upregulates the expression of programmed cell death 1 ligand 1 (PDL1) and indoleamine 2,3-dioxygenase (IDO) in macrophages, which inhibit NK cell-mediated and cytotoxic T lymphocyte-mediated cytotoxicity.

and reduces the number of repressor cells, resulting in an augmented immune attack against large established pancreatic tumours[163].

In general, GSDMD has been viewed as an executioner of pyroptosis downstream of caspase 1 and caspase 11. However, a recent study has demonstrated that apoptosis-inducing chemotherapies are capable of inducing pyroptosis by activating gasdermin E (GSDME) in a caspase 3-dependent manner[164]. On the basis of this finding, it would be expected that chemotherapy would be more effective in GSDME-expressing cancers. It is worth investigating whether GSDME-mediated pyroptosis is a preferred mode of cell death that subsequently activates inflammasomes in neighbouring cancer cells.

Inflammasome-targeting therapy

Multiple approaches can be used to target inflammasome activity, including abrogation of upstream signalling pathways, inhibition of inflammasome components and antagonism of end-products of inflammasome activation (TABLE 2). Pharmacological inhibition of the NLRP3 inflammasome has been widely implemented in laboratory studies, which have been reviewed elsewhere[165,166]. In clinical studies, cytokine blockade is the most successful approach, and evidence of the effectiveness of IL-1 inhibition in anticancer treatment is just emerging. A phase II clinical trial investigating the effect of the IL-1RA anakinra in patients with early-stage multiple myeloma indicates that IL-1RA suppresses markers of disease progression[167,168]. IL-1RA blocks signalling induced by both IL-1α and IL-1β. While the production of the latter cytokine is virtually inflammasome-dependent, studies have shown IL-1α release can be either dependent or independent of inflammasome activation[169]. A phase III trial of MABp1 (a monoclonal antibody targeting IL-1α) treatment in refractory CRC has shown clinical benefit and an increase in median survival[170]. This suggests that the efficacy of anakinra in cancer treatment may in part come from the inhibition of IL-1α.

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) was a clinical trial to determine whether IL-1β inhibition prevents cardiovascular events in patients who had high markers of inflammation after a myocardial infarction. In a secondary analysis, it was found that canakinumab reduced lung cancer incidence and mortality but did not affect other types of cancer[171]. The results are encouraging for cancers in which inflammation is highly involved in cancer development and progression. In a phase II trial for metastatic CRC, coadministration of anakinra with 5-FU and bevacizumab has shown a favourable median survival similar to that of other palliative therapies[172]. Therefore, targeted therapy against inflammasome activation could be useful in adjuvant or palliative therapies for cancer.

Conclusion

Understanding how inflammasome signalling affects tumour initiation and progression has been one of the most intriguing areas in the field. Inflammasomes exhibit distinct and sometimes conflicting roles in multiple facets of tumorigenesis. The influence of the inflammasome in tumour promotion ranges from suppressing antitumour immunity and cell death to fostering proliferation, angiogenesis and metastasis. The relative expression of inflammasome components differs in various cell types[4], which suggests that inflammasomes perform distinct functions in different cellular compartments. The tumour-suppressive function of the inflammasome is largely reflected in its preventive role in colitis and colon cancer, which is achieved by tumour immunosurveillance,

Canakinumab Anti-inflammatory Thrombosis Outcomes Study
(CANTOS). A randomized, double-blinded, placebo-controlled trial to evaluate the effect of canakinumab, a human monoclonal antibody that selectively neutralizes interleukin-1β (IL-1β), in the prevention of recurrent vascular events in patients with previous myocardial infarction.

Table 2 | **Therapeutic targets of inflammasomes in cancer**

Therapy	Inflammasome target	Cancer type	Clinical trial phase (ClinicalTrials.gov identifier)
Anakinra	IL-1β	Metastatic breast cancer	Phase I (NCT01802970)[203,204]
Anakinra	IL-1β	Metastatic CRC	Phase II (NCT02090101)[172,205]
Anakinra	IL-1β	Multiple myeloma and plasma cell neoplasm	Phase II (NCT00635154)[167,168,206]
Canakinumab (Ilaris)	IL-1β	CRC, breast cancer, NSCLC and adenocarcinoma	Phase I (NCT02900664)[207]
Thalidomide	Caspase 1	Multiple myeloma[208,209]	NA
MCC950	NLRP3	Head and neck SCC[210]	NA
Glyburide	NLRP3 (REF.[211])	NA	NA
BOT-4-one	NLRP3	Lymphoma[166]	NA
IL-18BP	IL-18 (REF.[89])	NA	
Methylene blue	NLRP3, AIM2 and NLRC4 (REF.[212])	NA	NA
CY-09	NLRP3 (REF.[213])	NA	NA

AIM2, absent in melanoma 2; CRC, colorectal cancer; IL-1β, interleukin-1β; IL-18, interleukin-18; IL-18BP, interleukin-18 binding protein; NA, not available; NSCLC, non-small-cell lung cancer; SCC, squamous cell carcinoma.

maintaining epithelial integrity, producing mucus and suppressing the proliferation of intestinal epithelial cells. Regardless of whether the dysregulated inflammasome signalling is a result of dysbiosis or vice versa, which has not been conclusively investigated yet, both affect intestinal inflammation and cancer development. In addition to genetic factors, environmental factors (for example, diet) and experimental conditions associated with animal models influence the ecology of the gut microbiota and, in turn, inflammasome activation.

Given that the outcomes of inflammasome signalling are diverse across tumour types, gaining insight into how to manage this diversity will be an important area for future investigations. Clinical trials that specifically inhibit inflammasome components in human cancers are yet to be performed (TABLE 2). Although a major clinical trial inhibiting the downstream effector molecule IL-1β has recently yielded promising results[171], blocking IL-1β or IL-18 individually is not the same as caspase 1 inhibition. Caspase 1 blockade can inhibit global inflammatory responses regulated by both inflammasome-dependent cytokines and pyroptosis. In addition, inhibition of a specific inflammasome like NLRP3 by MCC950 can block pathological effects of NLRP3 without compromising beneficial effects from other inflammasomes. Indeed, the development of highly specific NLRP3 inhibitors, such as MCC950, and caspase 1 inhibitors has opened exciting new avenues for translational research, with the potential for therapeutic targeting of tumorigenesis. The studies highlighted in this Review outline a roadmap for developing specific anticancer therapy by modulating inflammasome signalling, which could set the stage for the concept of tumour immunoediting by inflammasome signalling.

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