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Inflammasomes in breast cancer: the ignition spark of progression and resistance?

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Review

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Abstract

Inflammation and immune evasion are major key players in breast cancer (BC) progression. Recently, the FDA approved the use of anti-programmed death-ligand 1 antibody (anti-PD-L1) and phosphoinositide 3-kinase (PI3K) inhibitors against aggressive BC. Despite the paradigm shift in BC treatments, patients still suffer from resistance, recurrence and serious immune-related adverse events. These obstacles require unravelling of the hidden molecular contributors for such therapy failure hence yielding therapeutics that are at least as efficient yet safer. Inflammasome pathway is activated when the pattern recognition receptor senses danger signals (danger-associated molecular patterns) from damaged\dying cells or pathogen-associated molecular patterns found in microbes, leading to secretion of the active pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18). It has been shown throughout numerous studies that inflammasome pathway enhanced invasion, metastasis, provoked BC progression and therapy resistance. Additionally, inflammasomes upregulated the proliferative index ki67 and enhanced PD-L1 expression leading to immunotherapy resistance. IL-1β contributed to significant decrease in oestrogen receptor levels and promoted BC chemo-resistance. High levels of IL-18 in sera of BC patients were associated with worst prognosis. Stimulation of purinergic receptors and modulation of adipokines in obese subjects activated inflammasomes that evoked radiotherapy resistance and BC progression. The micro RNA miR-223-3p attenuated the inflammasome over-expression leading to lowered tumour volume and lessened angiogenesis in BC. This review sheds the light on the molecular pathways of inflammasomes and their impacts in distinct BC subtypes. In addition, it highlights novel strategies in treatment and prevention of BC.

Introduction

Breast cancer (BC) burden has surpassed lung cancer and was ranked the first diagnosed cancer globally and the first among females in Egypt according to GLOBOCAN 2020 (Refs 1, 2). BC molecular classification was grounded on the expression of hormone receptors (HRs) including oestrogen receptor (ER), progesterone receptors (PR), human epidermal growth factor receptors 2 (HER2) and the proliferative index Ki-67 (Ref. 3). Four main molecular BC subtypes have been extensively characterised comprising: luminal A (ER+/PR+/HER2–/lowKi-67) with best prognosis, luminal B (ER+/PR+/HER2–/+/high Ki-67), HER-2 enriched (ER–/PR–/HER2+) and finally the most aggressive triple-negative breast cancer (TNBC) subtype (ER–/PR–/HER2–) which is associated with worst prognosis (Refs 3, 4). Inflammation and immune evasion are major key players in BC progression that require urgent consideration (Ref. 5). In 1863, the pathologist Rudolf Virchow noticed the presence of large number of leucocytes infiltrating in tumour tissues and believed that cancer is similar to the process of wound healing in chronic inflammation (Ref. 6). More than a century later, Dvorak demonstrated that cancer is a wound that does not heal (Ref. 7). Further studies supported this belief and showed that approximately 25% of all human cancers in adults result from chronic inflammation (Ref. 8). Treatment with non-steroidal anti-inflammatory drugs such as, celecoxib; a cyclooxygenase-2 selective inhibitor, showed anti-tumour effects in primary BC tissue during clinical trial (Ref. 9). In chronic inflammation, immune cells generate high levels of cytokines in an uncontrolled manner such as tumour necrosis factor-α (TNF-α) that induce accumulation of reactive oxygen and nitrogen species which subsequently interact with DNA leading to permanent genomic alterations, initiation of tumours and malignant cell growth (Ref. 10). Malignant cells also interact with micro-environment via inflammation, where cancerous cells secrete cytokines, chemokines and transcriptional factors that are molecular players in the regulation of onco-genesis (Refs 11, 12).

It has been a mystery to distinguish between immunogenic and non-immunogenic cell death (ICD) (Ref. 13). Many years ago, it was believed that physiologic cell death (apoptosis), which occurs as a cellular byproduct turnover, does not cause any immune response (non-immunogenic) and that apoptotic cells are phagocytosed rapidly without causing inflammation or auto-immunity (Ref. 13). In 1994, Polly Matzinger proposed 'The Danger Model', which implies that the immune system is more concerned with damage than with foreignness (Refs 14, 15). Stressed, injured or dying cells were found to express their fear of danger by releasing mediators called 'danger-associated molecular patterns' (DAMPs) that warn the

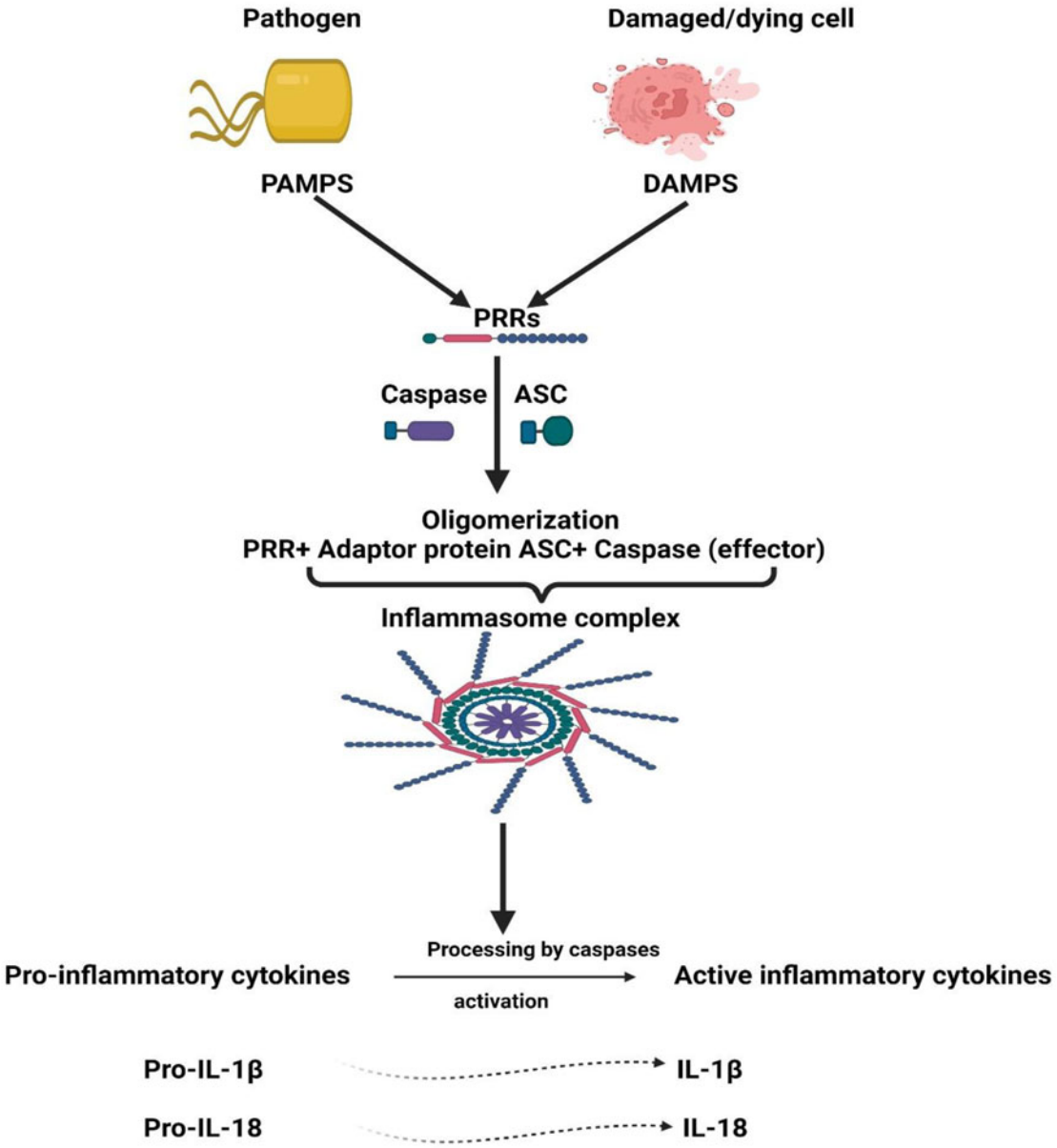

Figure 1. Inflammasome complex activation. Pattern recognition receptors sense the presence of PAMPs or DAMPs stimulating the recruitment of ASC/Caspase and their oligomerisation with PRR leading to the formation of inflammasome complex. The in-active pro-inflammatory cytokines (Pro-IL-1β and Pro-IL-18) are then cleaved by caspase into their active forms. PAMPs, pathogen-associated molecular patterns; DAMPs, danger-associated molecular patterns; PRR, pattern recognition receptors; ASC, apoptosis-related speck-like protein containing a CARD; IL-1β, interleukin 1β; IL-18, interleukin 18.

body about tissue injury or danger in these areas and trigger sterile inflammation (Refs 14, 15). In healthy cells, DAMPs are kept inside the cell (no inflammatory reaction) (Ref. 15). On the other hand, when the cells are in danger (stressed or dying), such as cancer cells exposed to radiation or some chemo-therapeutic agents like oxaliplatin or anthracyclines, induction of a specific form of apoptosis named ICD takes place by emission of DAMPs from apoptotic cells (Refs 16, 17). Inflammation is an innate defence mechanism (Ref. 18). Innate immune cells have pattern recognition receptors (PRRs) that are able to recognise molecules frequently found in microbes or released by injured/necrotic cells through their pathogen-associated molecular patterns (PAMPs) and DAMPs, respectively. Upon detecting DAMPs or PAMPs by PRR, inflammasomes are activated facilitating pyroptosis (a lytic programmed cell death) via induction of caspase 1 activation and the subsequent activation and release of interleukin-1β (IL-1β) and interleukin-18 (IL-18) (Ref. 18) (Fig. 1).

Throughout distinct studies, inflammasomes have been shown to take part in development of several inflammatory disorders like pancreatitis (Ref. 19) and might increase risk of cancer (Ref. 20). In addition, high concentration of pro-inflammatory cytokines IL-1β and IL-18 in tumour tissues was associated with increased carcinogenesis and poor prognosis (Refs 21, 22). In BC, high levels of ATP released from radiotherapy-resistant BC cells promoted inflammasome activation via purinergic receptors leading to increased invasion, angiogenesis and metastasis (Ref. 23). Nevertheless, literature reported that obesity increased the risk of BC development via increasing leptin and decreasing globular adiponectin, resulting in activated inflammasome and tumour growth (Ref. 24). Inhibition of the NLRP3 inflammasome via micro-RNA (miRNA) 223-3p lessened the growth and immunosuppression of human BC *in vitro* and *in vivo* (Ref. 25). Activation of AIM2 inflammasome and IL-1β secretion were reported to increase programmed death-ligand 1 (PD-L1) expression and subsequently, suppress anti-tumour immunity (Ref. 26).

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Blocking of IL-1β in mouse BC synergises the effect of anti-programmed death-1 (PD-1) and reversed immunosuppression (Ref. 27). Tecentriq® (Atezolizumab), the newly FDA-approved anti-PD-L1 antibody, to be used in combination with chemotherapy for the treatment of metastatic TNBC patients (Ref. 28), unfortunately showed modest response rates and was associated with serious immune-mediated adverse events (Ref. 29). Until date, there is no available anti-cancer drug that directly targets inflammasome pathway. This review highlights the effects of inflammasomes pathways in BC and its possible molecular targets, thus sheds the lights on novel strategies in the prevention and treatment of BC.

Literature search was done at the States National Library of Medicine (PubMed). The descriptors used for the search in databases were: 'inflammasome' and 'purinergic receptor' or 'P2Y1R' 'P2Y2R' or 'P2Y4R' or 'P2Y6R' or 'P2Y11R' or 'P2Y12R'or 'P2Y13R' or 'P2Y14R' or 'P2X1R' or 'P2X2R' or 'P2X3R' or 'P2X4R' or 'P2X5R' or 'P2X6R'or 'P2X7R' and 'breast cancer', 'adipokine' or 'leptin' or 'adiponectin' and 'inflammasome' and 'breast cancer', 'none coding RNA' or 'miRNA' or 'lncRNA' and 'inflammasome' and 'breast cancer', 'inflammasome' and 'immune check point' or 'PD-1' or 'PD-L1' or 'CTLA4' and 'breast cancer'. Published data, research papers and books were reviewed for their relevance to the aim of the review. The selection was done by reading abstracts first and then reading relevant full-text articles of relevant publications. Criteria for inclusion were: complete, relevant publications, available online, all years were included (no filters), in English, with detailed information about participants, methods and analyses. Criteria for exclusion: duplicate and out of scope publications. Data collection was done during December 2022, and data abstracted was in the form of descriptive information, covering the type of samples used, techniques and findings or effects reported. Bias was limited through the evaluation of the studies through their internal validity rather than the conclusion.

What are inflammasomes?

Inflammasome structure and activation

In 2002, Fabio Martinon was the first to identify the inflammasome complex (Ref. 30). From the name, it's an inflammatory signalling complex, located inside the cell (Ref. 18). The inflammasome is made up of a receptor that works as a sensor (PRR), the adaptor protein apoptosis-related speck-like protein containing a CARD (ASC) and the effector Caspase as reported by Jay Amin *et al.* (Ref. 18). Once PRR senses the presence of DAMPs or PAMPs, oligomerisation of inflammasome components occurs (PRRs and ASC), then ASC polymerises to form helical structure called ASC speck formation, which is essential for recruitment of caspase 1 (Ref. 31), that in turn cleaves and activates IL-1β and IL-18 (Ref. 32). Finally, cell membrane perforations and inflammatory programmed cell death called pyroptosis occur (derived from the Greek terms 'pyro', which means fire, and 'ptosis', refers to falling) (Ref. 33) (Fig. 1).

PRRs involved in formation of inflammasomes

PRRs recognise distinct ligands and can be classified according to its cellular location into transmembrane and cytoplasmic PRRs (Ref. 18). The transmembrane PRRs include Toll-like receptors and the C-type lectin receptors, while cytoplasmic PRRs encompass nucleotide-binding oligomerisation domain-leucine-rich repeats-containing receptors (NLR), retinoic acid-inducible gene-I-like receptors, absent-in-melanoma (AIM)-like receptors and pyrin inflammasome (Refs 18, 34).

ASC and caspases

ASC 'also called PYCARD' is responsible for the activation of caspases (Refs 35, 36), which are important for association and activation of inflammasome (Refs 36, 37, 38). Caspases are divided into apoptotic (e.g. caspase 8) and inflammatory caspases (e.g. caspases 1, 4 and 5) (Refs 36, 37, 38). According to the type of caspases involved, inflammasomes are divided into the canonical and non-canonical inflammasome (Refs 18, 39, 40). Caspase 1 is activated within canonical inflammasome while caspase 4/5 or 8 is involved in non-canonical inflammasome pathway (Ref. 41). Notably, the impacts of canonical and non-canonical inflammasome activation are similar; caspase-1 provokes activation of IL-1β, IL-18 and the release of danger signals, as well as pyroptosis, while caspase-4/5 promotes pyroptosis via cleavage of the pore-forming protein gasdermin D (GSDMD) and triggers a secondary activation of the canonical inflammasome and subsequent cytokine release (Ref. 41).

Inflammasome and its inflammatory cytokines in breast cancer

Inflammasome dual impacts in BC

Inflammasome is a double-edged weapon that exhibited dual roles in the modulation of BC tumourigenesis. NLRP3 activation contributed to immune system dysfunction, BC metastasis, invasion and migration (Ref. 42). NLR family pyrin domain containing 1 (NLRP1) expressing cells showed upregulated mesenchymal markers (Snail, MMP-9, Vimentin and C-myc), whereas epithelial markers (E-cadherin) were downregulated (Ref. 43). Moreover, NLR family CARD domain containing 4 (NLRC4) upregulated vascular endothelial growth factor A (VEGFA), resulting in angiogenesis induction and BC progression (Ref. 44). Elevated NLRP3 levels increased the expression of the proliferative index Ki67 in BC (Ref. 25). In addition, the relative mRNA expression of NLRP3 in BC cell lines (MDA-MB231, MCF-7 and SKBR3) was higher than normal mammary epithelial cells (Ref. 25). Knockdown of NLRP3 in MCF-7 cell lines repressed the expression of Ki67 and decreased immunosuppression (Ref. 45). NLRP3 was upregulated in TNBC cell lines leading to gemcitabine resistance and enhanced survival of BC cells (Ref. 46). NLRP3 inhibition reduced viability, colony formation and migration of TNBC cells (Ref. 47). Literature demonstrated that reactive oxygen species (ROS) can activate inflammasome pathway (Ref. 48). Interestingly, TNBC cell lines showed increased ROS levels that prolonged its survival (Ref. 49). ROS scavenging or repression in TNBC cell lines downregulated NLRP3 leading to inhibition of metastasis (Ref. 50), angiogenesis (Refs 51, 52), reduced migration and invasion (Ref. 53). On the contrary, ROS-activated inflammasome contributed to cell death of MDA-MB231 (Refs 51, 54). In addition, AIM2 suppressed proliferation of human BC (Ref. 55) and interferon-γ (IFNγ)-induced AIM2 activation promoted apoptosis in MCF-7 BC cells (Ref. 56). Collectively, the afore-mentioned opposing impacts of inflammasome in BC remain controversial and require further investigation.

*IL-1*β

IL-1β activation and secretion is primarily dependent on inflammasomes activation. In 1988, North *et al.* highlighted the ability of IL-1β to exert anti-tumour effects through inducing T-helper-1 (TH1) and T-helper-17 (TH17) responses (Ref. 57). In addition, literature reported that it served as an adjuvant for maturation and expansion of CD4+, CD8+ T cells and promoted adaptive T-cell-mediated immunity (Ref. 58). However, in BC, the high levels of IL-1β enhanced BC proliferation (Ref. 59) and were significantly associated with BC metastasis (Ref. 60) and invasion

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(Ref. 61). Moreover, IL-1β contributed to cisplatin resistance (Ref. 62) and doxorubicin resistance in BC cells (Ref. 63). In addition, IL-1β induced epithelial mesenchymal transition (EMT) and contributed to methylation of the ER 1 gene promoter. This epigenetic modification led to a significant decrease in ERα levels and promoted BC chemo-resistance (Ref. 64). Interestingly, after neoadjuvant chemotherapy (nCT), literature demonstrated that BC patients might experience change in their tumour subtype leading to adjuvant treatment alteration in 100% of such patients (Refs 65, 66, 67, 68). That's why HER2 and HR status (including ER and PR) should be evaluated not only before the initiation of nCT but also after nCT (Refs 65, 66, 67, 68). Since IL-1β contributed to a significant decrease in ERα levels (Ref. 64), further studies should be done to unravel the hidden reasons for such BC subtype conversion post nCT and whether inflammasome pathway and the subsequent IL-1β secretion were responsible for such change. Thus, targeting IL-1β might give promising effects in counteracting ER lowering, chemo-resistance and BC progression.

IL-18

In 1989, IL-18 was first identified as a factor that enhanced IFNγ production from TH1 cells (IL-18 is also known as IFNγ-inducing factor) (Ref. 69). Similar to IL-1β, it is cleaved and activated by caspase 1. It is produced from a wide range of normal and cancer cell types, where it binds to IL-18 receptor. Its activity is suppressed by the naturally occurring high-affinity IL-18-binding protein that inhibits its binding to IL-18 receptor (Refs 70, 71). IL-18 has opposing effects in BC. For instance, intra-peritoneal injection of IL-18 suppressed metastasis of BC to bones (Ref. 72) and canine IL-18 induced apoptosis in BC cells (Ref. 73). In addition, mesenchymal stem cells suppressed BC proliferation via IL-18 expression *in vitro* (Ref. 74). Contrarily, literature demonstrated IL-18 as a pro-oncogenic cytokine (Ref. 75) where its expression in BC led to enhanced invasion, metastasis (Refs 76, 77, 78, 79, 80, 81), migration (Refs 76, 82), proliferation (Ref. 83), angiogenesis (Ref. 84) and progression (Refs 85, 86). Interestingly, polymorphism in IL-18 contributed to BC among postmenopausal women (Ref. 87). IL-18-rs1946518, IL-18-607 and IL18-137 gene polymorphisms were significantly correlated with increased risk of BC (Refs 88, 89, 90, 91). It's also worth mentioning that IL-18 was overexpressed in tumour samples (Refs 92, 93), plasma (Ref. 94), saliva (Ref. 77) and sera (Ref. 85) of BC patients compared with control. IL-18 was associated with worst prognosis (Refs 21, 95) and its low expression represented better survival (Ref. 96). In addition, it contributed to doxorubicin resistance (Ref. 97). Combining chemotherapeutics with IL-18-targeted therapy is highly promising since it has been noticed that low levels of plasma IL-18 were predictive of excellent long-term survival in metastatic BC during chemotherapy (Ref. 98).

Purinergic receptors and inflammasomes in breast cancer

ATP release and purinergic receptors

Purinergic receptors are found in all cell types (Ref. 99) and are implicated in learning, memory, behaviour, sleep (Ref. 100), vascular contractility, immune function and growth (Ref. 101). Recently, there is increasing interest in the involvement of purinergic signalling in Corona virus disease 2019 (Covid-19) hyper-inflammation, and thrombosis (Ref. 102). In addition, purinergic receptors were over-expressed in various tumours and regulated proliferation in lung, bladder, prostate tumours (Refs 103, 104, 105) and have been associated with enhanced BC growth and invasion (Ref. 106).

Intracellular ATP is produced by mitochondria as a source of energy (Ref. 107). Damaged cells/tumour cells release ATP outside the cell where it acts as a DAMP (Ref. 107). In 1999, it was stated that TNF-α, which was highly abundant in tumour micro-environment, has shown to enhance tumour progression (Refs 108, 109) and metastasis (Ref. 110). Literature showed that TNF-α enhanced ATP release, especially in MDA-MB231, and it is radiotherapy resistant (RT-R-MDA-MB231) (Ref. 23).

The extracellular ATP activates its purinergic receptors (present on adjacent cells) via binding either to the seven P2X ion channel receptors subtypes (P2X 1–7) or the eight known P2Y G-protein coupled receptors subtypes (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13 and P2Y14) (Ref. 107).

P2Y purinergic receptors in BC

Several studies demonstrated various tumour-promoting effects of P2Y receptors in BC (Refs 111, 112, 113, 114, 115, 116, 117). P2Y1, P2Y6 and P2Y11 inhibition blunted BC metastasis and migration (Refs 111, 112, 116). In addition, the P2Y1 antagonist MRS2179 lessened BC growth (Ref. 113) and inhibited angiogenesis via blocking activation of vascular endothelial growth factor receptor 2 (VEGFR-2) (Ref. 114). The phosphoinositide 3-kinase (PI3K)/protein kinase B (also known as AKT; PI3K/AKT) pathway is a regulator of pivotal cell functions such as cell proliferation and survival (Ref. 118). Literature showed that ATP modulation of P2Y2/4 receptors increased BC proliferation via activation of the PI3K/AKT signalling pathway (Ref. 115). P2Y12 inhibition with ticagrelor (TIC) reduced spontaneous platelet aggregation/activation in BC patients and inhibited formation of large tumour cell-induced platelet–platelet aggregates (Ref. 117).

Expression of P2Y2R and inflammasomes in breast cancer

Findings indicated that P2Y2R expression was higher in tumour tissues of BC patients compared with normal epithelial tissues (Ref. 106). In addition, the highly metastatic BC cells (MDA-MB-231) secreted higher ATP and showed elevated P2Y2R activity than low metastatic (MCF-7) BC cells (Refs 23, 119, 120) and was associated with tumour progression, invasion and metastasis (Refs 106, 119, 120, 121). Interestingly, comparing MDA-MB231, MCF-7 and T47D with their radiotherapy-resistant BC cells (RT-R-MDA-MB231, RT-R-MCF7 and RT-R-T47D) showed that the radiotherapy-resistant BC cells released higher ATP than other BC cells (Ref. 23); whereas RT-R-MDA-MB231 BC cells showed highest P2Y2R activity and invasiveness (Ref. 23). Similarly, mRNA levels of NLRP3, NLRC4, ASC, cleaved caspase1 and IL-1β were higher in radiotherapy-resistant BC cells and showed enhanced invasiveness compared to MDA-MB-231 cells (Ref. 122). However, the expression of NLRP1 and AIM2 was lower in RT-R-MDA-MB231 than MDA-MB231 (Ref. 122).

Inflammasome components regulated by P2Y2R activation in breast cancer

Treatment with ATP triggered elevation of P2Y2R activity in MDA-MB231, MCF-7, T47D and their radiotherapy-resistant BC cells (Ref. 122) leading to increased invasiveness (Refs 23, 122). In MDA-MB231 and RT-R-MDA-MB231 BC cells, TNF-α or ATP treatment led to a significant increase in NLRC4, ASC and IL-1β protein levels in a P2Y2R-dependent manner (Ref. 122). Interestingly, MDA-MB231 and RT-R MDA-MB231 transfected with siRNA P2Y2R or apyrase (hydrolyses extracellular nucleotides) significantly lowered the increased caspase 1 activity, IL-1β and protein expression of NLRC4 and ASC (Ref. 122) that was triggered by TNF-α or ATP in both cells (Ref. 23).

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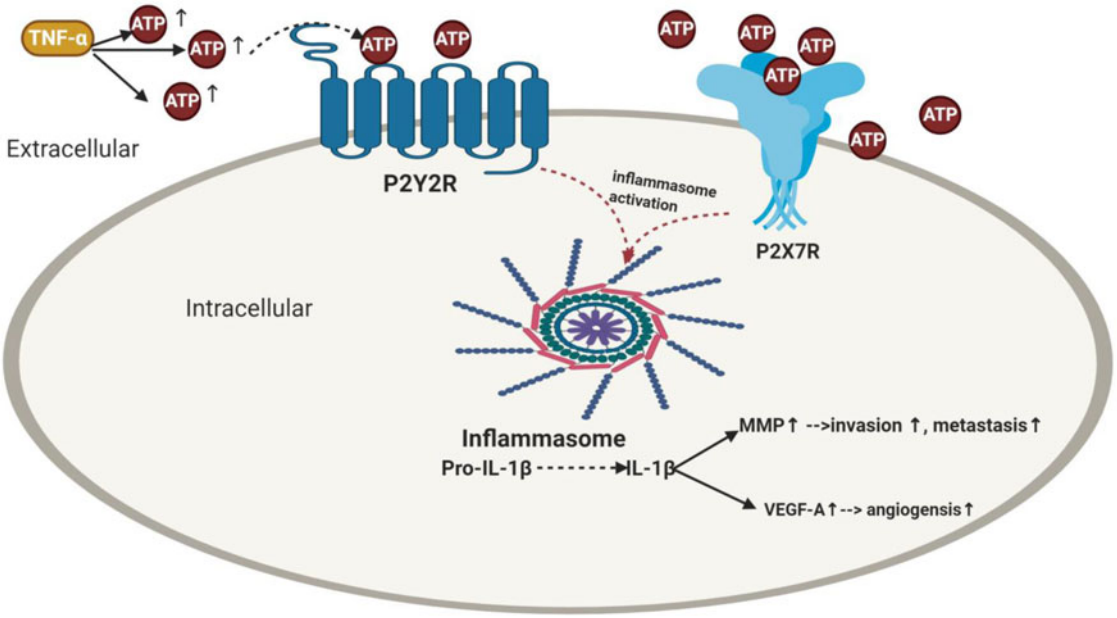

Figure 2. Impact of purinergic receptors on inflammasome activation in breast cancer and its correlation with angiogenesis, invasion and metastasis. TNF-α enhances ATP release. The extracellular ATP activates its purinergic receptors via binding either to the P2X7R receptors or P2Y2R provoking activation of inflammasome as well as IL-1β release which then elevates the levels of MMP and VEGF-A leading to BC metastasis and angiogenesis. TNF-α, tumour necrosis factor-α; ATP, adenosine triphosphate; IL-1β, interleukin-1β; MMP, matrix metalloproteinases; VEGF-A, vascular endothelial growth factor A.

Inflammasome activation induced invasion and angiogenesis in a P2Y2R-dependent manner in breast cancer

ATP increased the invasiveness in all radiotherapy-resistant BC cells in a P2Y2R-dependent manner where RT-R-MDA-MB231 showed the highest invasiveness (Ref. 23). Previous literature showed that IL-1β production would increase constantly until late time after stimulation with ATP (Ref. 23) for many reasons; IL-1β is not only produced by inflammasome activation (Ref. 23). In 1997, Ferrari *et al.* showed that ATP-induced IL-1β production (Ref. 123) via activation of nuclear factor-κB (NF-κB) (Ref. 124) is a critical regulator of fundamental cell functions, such as cell survival and proliferation (Ref. 125). In addition, the released IL-1β was found to promote the production of pro-IL-1β by binding to IL-1 receptor, which is expressed in various BC cells including MDA-MB231 (Ref. 126). Literature reported that matrix metalloproteinase (MMP) promotes tumour invasion and metastasis by inducing EMT in BC (Ref. 127). Furthermore, Yokoo *et al.* reported that the released IL-1β caused MMP production (Ref. 128), which was supported further by Amin *et al.* (Ref. 129). Similarly, Jin *et al.* supported these findings, where TNF-α and ATP increased MMP-9 activity in MDA-MB-231 and RT-R-MDA-MB-231 cells (Ref. 23) (Fig. 2). Similarly, in RT-R-MDA-MB231 and MDA-MB231 BC cells, ATP treatment markedly induced the secretion of VEGFA (Ref. 122), which is known to be produced by hypoxic tumour cells to induce angiogenesis and survival through binding to VEGFR (Refs 130, 131, 132, 133).

Inflammasome/P2Y2R inhibition lessened invasion, angiogenesis and tumour progression in BC

Accumulating evidence showed treating MDA-MB231 and RT-R-MDA-MB231 BC cells with caspase-1 inhibitor or P2Y2R siRNA abolished the MMP-9 activity (Ref. 23). Moreover, knockdown of P2Y2R or NLRC4, ASC and caspase-1 by siRNA decreased VEGFA production and suppressed the enhanced ATP-induced invasiveness (Ref. 122). Furthermore, addition of selective irreversible caspase-1 inhibitor (Ac-YVAD-CMK) or siRNAs of NLRC4, ASC and caspase 1 inhibited the invasiveness (Ref. 122) and colony formation (Ref. 23). In an *in vivo* P2Y2R-knockdown mouse model (RT-R-MDA-MB231-shRNA), results showed that RT-R-MDA-MB231-shRNA exhibited decreased tumour volume, increased body weight and significantly lowered IL-1β compared to cells transfected with empty vector (Ref. 23). Nonetheless, cells that transfect with empty vector showed higher MMP-9 compared to the P2Y2R knocked down group. From the above-mentioned, it is clear that inflammasome causes tumour progression in RT-R BC through P2Y2R (Ref. 23) (Fig. 2).

A wrap-up and insights

NLRP1 has been shown to promote BC cell proliferation, invasion and migration through inducing EMT (Ref. 43), but unfortunately, the exact molecular mechanism relating the NLRP1 to EMT was not elucidated. It would be worth to investigate the effect of ATP on P2Y2R or NLRP1 activation as well as MMP levels and its relation to EMT. Moreover, since literature showed that NLRC4 increased secretion of VEGFA and its knockdown decreased VEGFA level (Ref. 122), it would be interesting to examine the impact of P2Y2R or NLRC4 knockdown together with sorafenib (a multi-kinase inhibitor of tumour-cell proliferation and angiogenesis), since NLRC4 knockdown might potentiate sorafenib's anti-angiogenic effect.

In BC, the PI3K/AKT deregulation via mutations in PIK3CA gene or inactivation of the tumour suppressor phosphatase and tensin homologue deleted on chromosome 10 (PTEN) have been common in ER+ and TNBC patients, respectively (Refs 134, 135). Distinct studies reported that PI3K/AKT increased levels of MMP (Refs 136, 137). Recently, FDA approved the use of the oral PI3K inhibitor alpelisib (Piqray) in the treatment of HR+ metastatic BC patients with mutated PIK3CA (Ref. 138). Literature reported that ATP modulation of P2Y2 and P2Y4 receptors increased BC proliferation via activation of the PI3K/AKT signalling pathway (Ref. 115). In addition, NLRP3 knocked out mice showed an inhibition of the PI3K/AKT/mTOR pathway (Ref. 139). Since literature showed that P2Y2R signalling activated NLRC4 inflammasome in BC

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(Ref. 122), there is an urgent need to examine the impact of P2Y2R/NLRC4 and P2Y2R/NLRP3 on PI3K/AKT pathway. In addition, the synergistic impact of combining the P2Y2 antagonist (AR-C118925) or PSB-16133 (P2Y4R antagonist) (Ref. 140) together with alpelisib should be explored in BC. Mammalian target of rapamycin (mTOR) is a master regulator of intracellular metabolism and immune cell activation (Ref. 141) and its sustained activity has been shown to provoke resistance to alpelisib (Ref. 142) and endocrine treatment in BC (Ref. 143). Stimulation of the P2Y12R receptor led to the activation of mTOR via PI3K-AKT in vascular smooth muscle cells (Ref. 144) highlighting the possible role of P2Y12R signalling in alpelisib resistance. P2Y12R receptor inhibitors, such as clopidogrel (CDL) and TIC, were recommended in the treatment of acute coronary syndromes (Ref. 145). It would be interesting to examine the impact of TIC/CDL in alpelisib-resistant BC patients.

Interestingly, platelet aggregations have been associated with tumour evasion, and studies reported that platelets form aggregates with tumour cells creating a 'cloak' that shields the tumour cell from immune detection (Ref. 146). In BC, TIC inhibited the formation of large tumour cell-induced platelet–platelet aggregates in advanced metastatic BC patients (Ref. 117) and inhibited metastasis (Ref. 147). Moreover, CDL enhanced the toxicity of docetaxel and increased antitumour and/or anti-metastatic action of chemotherapeutics such as cyclophosphamide, 5-fluorouracil and mitoxantrone (Ref. 148), in contrast it decreased the anticancer activity of doxorubicin, cisplatin and tamoxifen (Ref. 148). Inhibitory impact of CDL and TIC on NLRP3 was investigated (Refs 149, 150). Oral administration of TIC strongly inhibited NLRP3 activation in peripheral blood mononuclear cells from patients with acute coronary syndrome (Ref. 150). In addition, CDL inhibited NLRP3 activation in rats (Ref. 149). Thus, collectively, these findings suggest the multi-strike clinical use of P2Y12R inhibitors in BC patients with cardiovascular diseases.

P2X7R and inflammasomes in breast cancer

P2X expression in breast cancer

Literature reported that the expression of P2X7R was elevated in breast tissue undergoing malignant change (Ref. 151), where all epithelial cells in all cases of *in situ* or invasive lobular or ductal carcinoma showed intense P2X7R while normal epithelium was devoid of the cytolytic P2X7R (Ref. 151). Interestingly, invasive epithelial cancer cells showed intense cell surface P2X7R receptors, whereas *in situ* lobular and ductal cases labelled P2X7R intracellularly (Ref. 151).

P2X opposing impacts in BC

Silencing of P2X5 receptors inhibited cell proliferation, metastasis and vimentin (an EMT marker) in MDA-MB-468 BC cells (Ref. 152). As for P2X7R, various studies have shown that it was highly expressed in BC tissues rather than normal ones (Refs 151, 153, 154). P2X7 receptor activation in MDA-MB-435s BC cell line led to increased migration and metastasis (Ref. 155). ATP released by dying cells activated P2X7R leading to invasive BC phenotype via AKT phosphorylation and NF-κB translocation to the nucleus (Ref. 156); which comprises a family of transcription factors and showed major roles in the development and progression of various cancers (Ref. 157). Another study came in accordance and showed that high expression of P2X7R in T47D BC cells increased invasion, migration and EMT through AKT phosphorylation (Ref. 158). This was further supported; P2X7 receptor downregulated the protein expression of E-cadherin and upregulated the production of MMP-13 via AKT pathway (Ref. 159). Moreover, treatment of P2X7R-positive MDA-MB-435s BC cells with the anthraquinone derivative emodin suppressed invasiveness via antagonising P2X7R *in vivo* (Ref. 160). Furthermore, P2X7R inhibition effectively induced apoptosis in MCF-7 BC cells (Ref. 153). Contrarily, ATP-P2X7R activation inhibited BC cell migration (Ref. 161); these conflicting impacts of P2X7R in BC require closer investigation.

P2X/inflammasomes opposing effects in breast cancer

Suppression of P2X7R expression by the natural isoquinoline alkaloid 'berberine' inhibited mRNA and protein levels of NLRP3 that consequently decreased cell viability, colony formation and migration of MDA-MB231 cells in a dose-dependent manner (Fig. 2) (Ref. 47). The role of P2X7R/NLRP3 in bone cancer pain was investigated; Walker-256 BC cells were injected into the tibia of female rats; P2X7R inhibition suppressed the expression of NF-κB, NLRP3/IL-1β signalling and suppressed bone cancer pain *in vivo* (Ref. 162). On the other hand, Ghiringhelli *et al.* demonstrated that P2X7R/NLRP3 activation showed anti-tumour effects (Ref. 163); the study demonstrated that ATP stimulated-P2X7R then triggered NLRP3 activation in dendritic cells (Ref. 163). Furthermore, chemotherapy was inefficient against tumours with P2X7R (−/−) or NLRP3(−/−) or Caspase-1(−/−) (Ref. 163). Additionally, BC patients bearing a loss of function allele of P2X7R treated with anthracycline developed metastatic disease more rapidly compared to those carrying the normal allele (Ref. 163).

Wrap-up and future insights

NF-κB played a critical role in endocrine resistance (Ref. 125), promoted human BC proliferation and migration via MMP-9 production *in vivo* (Ref. 125). It is worth mentioning that NF-κB is pivotal in the transcription and priming step of NLRP3 activation (Ref. 164). On the other hand, NLPR3 also activated NF-κB where its knocking down reduced NF-κB activation in both sterile and microbially induced inflammation (Ref. 165). Since P2X7R inhibition suppressed the expression of NF-κB and NLRP3 in rats (Ref. 162), it would be interesting to examine the impact of P2X7R/NF-κB/NLRP3 in BC as their concomitant inhibition might be eminent in counteracting BC resistance and progression. ATP-P2X4 signalling mediated NLRP3 inflammasome activation: a novel pathway of diabetic nephropathy (Ref. 166). Suramin is an old drug that is still being used to treat the first stage of acute human sleeping sickness (Ref. 167) and has been shown to be an antagonist of ATP at P2X purinergic receptors (Ref. 168). Recent literature reported that it inhibited ATP-induced NLRP3 complex formation, caspase-1 and IL-18 expression in mice mesangial (Ref. 169). It would be advantageous to examine the impact of P2X4/NLRP3 in BC. In addition, the potential role of suramin on P2X/NLRP3 inhibition should be investigated in BC.

Simvastatin (SIM), a hypocholesterolemic drug, was shown to inhibit P2X7 receptor, NLRP3 inflammasome, IL-1β and IL-18 in rats (Ref. 170). Studies reported that SIM showed cytotoxic effects against MDA-MB231 and MCF-7 BC cell lines (Ref. 171). Recent literature stated that SARS-CoV-2 infection triggered extracellular ATP elevation, P2X7 receptors stimulation and NLRP3 inflammasome hyperactivation causing neurological complications in Covid-19 patients (Ref. 172). Thus collectively, SIM might show beneficial impacts in SARS-CoV2-infected BC patients. P2X7R showed opposing effects in cancer. Literature reported that P2X7R showed anti-tumour effects and was required for priming of tumour antigen-specific CD8 + T cells via activation of NLRP3, Caspase 1 and the subsequent release of Il-1β (Ref. 173). Furthermore, in fibrosarcoma cells, antineoplastic mitoxantrone-treated mice triggered a protective immune response preventing tumour growth, but this protective effect was abolished in

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P2X7R-deficient mice (Ref. 173); these conflicting effects require closer investigation. A study demonstrated that released ATP had a biphasic effect on invasion and metastasis of MDA-MB-231 BC cell line; where low ATP doses induced inhibition, while high doses induced promotion (Ref. 174); this might be an explanation for the aforesaid conflicting impacts of P2X receptors in BC. Literature reported that, ATP-high MDA-MB-231 BC cells possessed a dramatic increase in their ability to metastasise in a preclinical model *in vivo* (Ref. 175). In addition, metastasis was largely prevented by treatment with an FDA-approved mitochondrial ATP-synthase inhibitor, (bedaquiline) (Ref. 175). These results give a hint on investigating the impact of bedaquiline on purinergic receptors/inflammasome/MMP in BC patients and its possible use as an anti-metastatic agent in BC

Inflammasome pathway and immune check points in breast cancer

Under normal physiological conditions after tumour destruction and clearance, immune checkpoints act as 'brakes' that are involved in maintaining immune homeostasis and also protect against tissue damage and auto-immunity (Ref. 176). The expression of immune checkpoint proteins can be dysregulated by tumours as an important immune resistance mechanism that ease tumour evasion from anti-tumour immunity and subsequently leading to cancer progression (Refs 177, 178). In 2018, Dr James P Allison and Dr Tasuku Honjo were awarded Nobel Prize in Physiology or Medicine for their respective discoveries of the immune checkpoint proteins cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4) and PD-1 (Refs 179, 180). The PD-1 binds to its ligand; PD-L1 then delivers inhibitory signals to T cells leading to T-cell exhaustion and deactivation (Ref. 181). Interestingly, immune check points inhibition (ICI) by monoclonal antibodies (mAb) have led to a surge in the treatment of solid tumours (Refs 179, 180). However, many patients can acquire resistance and immune-related adverse events (irAE) over time (Refs 182, 183). There is now an urgent need to investigate mechanisms of resistance and irAE. Several studies showed that inflammasome pathway led to immunosuppression (Refs 184, 185, 186).

Immune check points in BC

PD-1/PD-L1 and CTLA-4 expression in BC

Generally speaking in BC, the expression of PD-L1 has been associated with large tumour size, high proliferation, high-grade, ER-negative status and HER2-positive status (Ref. 187). In light of the fact that BC is highly heterogeneous, PDL-1/PD-1 expression may vary among different molecular subtypes (Refs 188, 189). Interestingly, several studies reported that PD-L1 expression is more commonly found in the more immunogenic subtypes including TNBC and HER2 positive BC (Refs 188, 189). On the contrary, a study of 1091 BC patients, the expression rate of PD-L1 in luminal A was higher than that of the other BC subtypes (Ref. 190). As for PD-1, its highest expression was higher in the basal-like subtype compared to luminal A with lowest PD-1 expression (Ref. 191). Another study showed that in TNBC, the expression rates of PD-L1 and PD-1 were significantly higher than the expression in other subtypes (Ref. 192). CTLA-4 expression in blood of BC patients was seven folds higher than that of healthy donors (Ref. 193). High expression of CTLA-4 was frequently identified in TNBC and HER2+ (Ref. 194).

Inflammasomes and PD-1/PD-L1 in BC

Literature showed that high peripheral levels of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSC) correlate with increased tumour angiogenesis, higher tumour grade, tumour promotion and T-cell-mediated suppression by blocking the development of an effective antitumour immunity (Ref. 195). A recent study reported that genetic and pharmacologic inhibition of NLRP3 blocked PMN-MDSC accumulation in the lung in response to anti-PD-1 therapy and inhibited metastatic progression in preclinical BC models (Ref. 196). Under hypoxic conditions in MDA-MB231 PD-L1 translocated to the nucleus (nPD-L1) upon TNF-α treatment. nPD-L1 enhanced the transcription of the gasdermin C (GSDMC) and its cleavage by caspase 8 causing non-canonical pyroptosis which was associated with BC poor prognosis in nude mice (Ref. 197). Since cleavage of the pore-forming protein GSDMD triggered a secondary activation of the canonical inflammasome (Ref. 41), the involvement of PD-L1/GSDMC/canonical inflammasome activation warrants investigation. Another study demonstrated that AIM2 inflammasome upregulated PD-L1 via IL-1β leading to immunosuppression in BC whereas neutralisation of IL-1β significantly suppressed PD-L1 (Ref. 26) (Fig. 3). Similarly, blocking IL-1β in mouse BC reversed immuno-suppression and synergised the effect of anti PD-1 (Ref. 27). In TNBC cells, tumour-derived IL-18 induced PD-1 expression on immunosuppressive NK and in B cells (Refs 198, 199).

Inflammasomes and CTLA-4 in BC

Little is known about the impact of inflammasomes on CTLA-4. However, in May 2022, Khandekar *et al.* demonstrated that BC-bearing mice in high salt diet cohort coupled with anti-CTLA-4 mAb showed upregulated NLRP3 complex activity leading to irAE while downregulated NLRP3 diminished irAE in low salt diet cohort plus anti-CTLA-4 mAb, suggesting the involvement of NLRP3 pathway in irAE which is a major clinical challenge in the treatment with ICIs (Ref. 200).

Wrap-up and insights

TNF-α led to the stabilisation of PD-L1 via NF-κB in BT549 TNBC cell line (Ref. 201). In addition, TNF-α enhanced ATP release in MDA-MB231/RT-R-MDA-MB231 (Ref. 23) and activated P2Y2R/NLRC4 leading to enhanced invasiveness (Ref. 122). Moreover, TNF-α blockade synergised with anti-PD-1 (Ref. 202). Thus, there might be a link between the effects of NF-κB/TNF-α/ATP release, P2Y2R/NLRC4 and PD-L1 immunosuppression to be urgently investigated. Also, the effects of apyrase, or P2Y2R antagonist/siRNA or caspase 1 inhibitor and their impacts on PD-1 expression in BC cells are quite promising to be explored. Examining the effects of the above-mentioned players in TNBC cells treated with atezolizumab is also tempting since inhibition of ATP/P2Y2R/NLRC4 pathway might possess a synergistic effect. Thus, development of a new combination therapy, lowering the needed concentration of atezolizumab and consequently, ameliorating irAEs.

Several studies showed that inflammasome pathway led to immunosuppression (Refs 184, 185, 186). In addition, NLRP3 inflammasome promoted the expression of PD-1 in head and neck squamous cell carcinoma (Ref. 184) and PD-L1 in pancreatic cancer (Ref. 203). Interestingly, not only NLRP3 promoted the expression of PD-1 or PD-L1 but also tumour PD-L1 activated NLRP3 inflammasome leading to resistance in response to PD-1 blockade in advanced melanoma (Ref. 185). Surprisingly, PD-1/or PD-L1 immunotherapy blockade also activated NLRP3 inflammasome that recruited myeloid-derived suppressor cells (MDSCs) causing immunotherapy resistance (Ref. 185). In asymptomatic multiple myeloma, these results were further supported in human DCs where PD-L1 blockade activated NLRP3 and increased caspase-1 (Ref. 186) (Fig. 4). Collectively, NLRP3 and PD-1/PD-L1 create an immunosuppressive loop leading to

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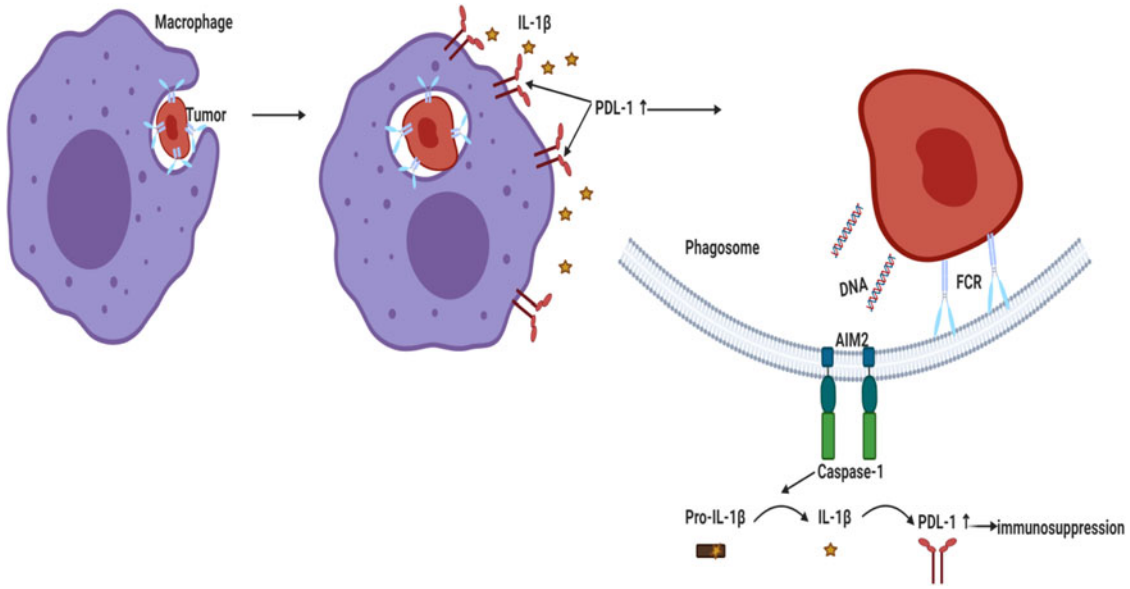

Figure 3. Activation of AIM2 inflammasome led to PD-L1 upregulation and immunosuppression in BC. Phagocytosed tumour DNA activated AIM2 inflammasome leading to IL-1β secretion that upregulated PD-L1 and enhanced immunosuppression. AIM2, absent in melanoma 2; PD-L1, programmed death ligand 1; IL-1β, interleukin-1β.

immunotherapy resistance that warrant closer investigation in BC. Activation of AIM2 led to PD-L1 upregulation and immunosuppression in BC (Ref. 26). In addition, cisplatin increased the expression levels of PD-L1 (Ref. 204). Thus, it would be interesting to investigate the effect of siRNA AIM2 in combination with cisplatin and PD-1/PD-L1 blockade in BC since it might be a promising solution to immune checkpoint resistance and the tumour-associated immunosuppressive effects.

Studies showed that inflammasome activation increased the secretion of IL-1β that subsequently elevated MMP-9 (discussed in purinergic part) (Ref. 23). Furthermore, MMP-9 inhibition coupled with anti-PD-L1 increased TCR diversity and TH-1 response in tumours (Ref. 205). Interestingly, tumour cells not only express PD-L1 on its surface but also can secrete a soluble form of PD-L1 with an immunosuppressive function (Ref. 206) that can be generated by cleavage from cell surface by MMP (Ref. 207). In 2020, a study reported that secreted PD-L1 could be used as a non-invasive biomarker for evaluating the malignancy of TNBC and predicting the response to nCT (Ref. 208). In addition, there was a significant correlation between tumoural PD-L1 and the soluble PD-L1 in the serum of BC patients (Ref. 209). Furthermore, high levels of soluble PD-L1 in peripheral blood were associated with poor prognosis (Ref. 209). Hence, it would be tempting to explore the impact of inflammasome/MMP and soluble PD-L1 in BC.

Blocking IL-1β in mouse BC reversed immunosuppression and synergised the effect of anti PD-1 (Ref. 27). Similarly, IL-18 induced PD-1 expression in BC (Refs 198, 199). Thus, targeting inflammasome complex and its downstream cytokines might counteract metastasis and PD-1/PD-L1 immunotherapy resistance. It has been noticed that cells treated with IL-12/15/18 cytokines induced cell surface expression of CTLA-4 on

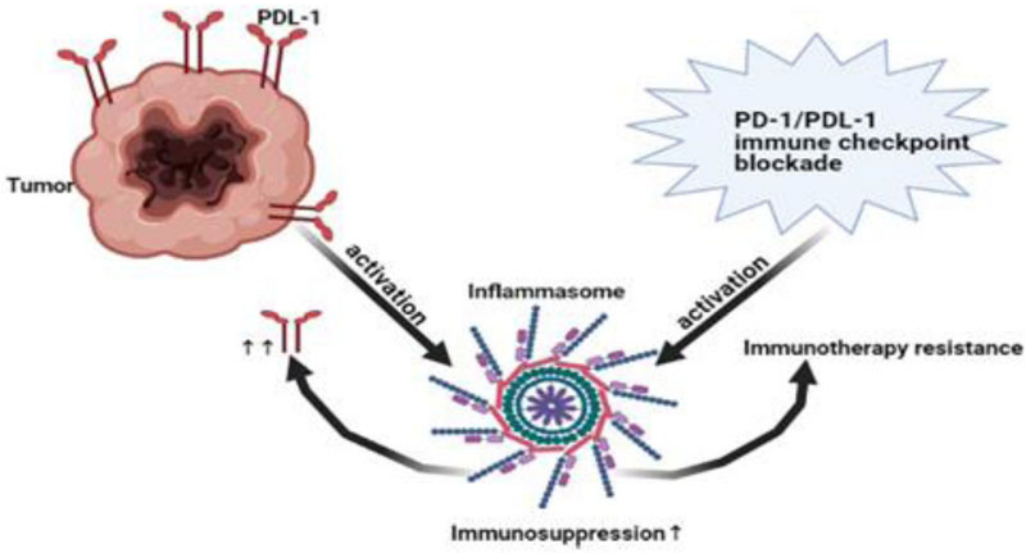

Figure 4. Immunosuppressive loop of NLRP3/PD-L1. NLRP3 promoted immunotherapy resistance via expression of PD-1/PD-L1. On the other hand, tumoural PD-L1 and even PD-1/PD-L1 blockade activated NLRP3 leading to immunotherapy resistance and immunosuppression. Thus, NLRP3 pathway and PD-1/PD-L1 are key characteristic for immunotherapy resistance. PD-1, Programmed death1; PD-L1, programmed death ligand 1; NLRP3, NOD-like receptor (NLR) family, pyrin domain-containing protein 3.

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mucosal-associated invariant T independent of TCR signal (Ref. 210). Since NLRP3 activation and irAE occurred post CTLA-4 mAb in BC-bearing cohort (Ref. 200), NLRP3/IL-18/CTLA-4 and irAE warrant closer investigation in BC.

Adipokines and inflammasomes in breast cancer

Obesity is a risk factor for developing different types of cancers including BC and is associated with a worse clinical outcome (Ref. 211), especially in postmenopausal women (Refs 212, 213, 214). Obesity symbolises a chronic low-grade inflammatory condition, which causes elevation in the circulating pro-inflammatory cytokines that recruit macrophages into adipose tissue, subsequently leading to dysregulated secretion of adipokines (cytokines derived from adipose tissue) (Ref. 215).

Adipokines include leptin and adiponectin, their plasma ratio is considered a biomarker for initial cancer development and progression (Ref. 216). Leptin is principally secreted by adipocytes to suppress appetite, food intake and regulate body weight by acting on hypothalamus (Refs 217, 218). It is associated with obesity since the higher the adipose tissue mass, the more secreted leptin levels (Refs 217, 218). On the other hand, adiponectin and adiposity are inversely correlated, where adiponectin levels decrease in obese subjects (Ref. 219). Interestingly, adiponectin and leptin elicit opposing effects, where leptin showed pro-inflammatory properties inducing the production of IL-6 and TNF-α (Refs 220, 221), while adiponectin is an anti-inflammatory agent (Ref. 222). In addition, adiponectin markedly suppressed mRNA of leptin and its receptor. On the other hand, leptin also markedly downregulated adiponectin receptor 1 (adipoR1) mRNA expression in BC (role of adipoR will be discussed in adiponectin part) (Fig. 5).

Collectively, adiponectin and leptin can antagonise each other at the transcriptional level of their receptors or at the level of adipokines production (Ref. 223). Notably, the reduced expression of adiponectin receptors or low plasma levels of adiponectin has been linked to increased risk of certain types of cancers (Refs 224, 225). It has been reported that adiponectin exerts antitumour activities, while leptin promotes tumour growth (Refs 226, 227, 228) and it was correlated with hypertension, angiogenesis, atherosclerosis and ROS generation (Ref. 229). Interestingly, ER signalling plays an important role in proliferation and survival of BC cells through ROS production (Ref. 230). Leptin activates ER signalling without ligand via a process called transactivation, where leptin activates ERα through mitogen-activated protein kinases pathway (Ref. 231).

Leptin and inflammasomes in breast cancer

Impact of leptin on NLRP3 in ER+/ER– breast cancer subtypes

In ER + BC cells (T47D and MCF-7), leptin upregulated NLRP3, ASC expression as well as ASC speck formation, caspase-1 and IL-1β generation (Ref. 24). Literature showed that ER played a pivotal role in survival and proliferation of BC cells through ROS production (Ref. 230). In MCF-7 BC cells, leptin rapidly increased ROS production that caused NLRP3 activation (Ref. 24). Nevertheless, pre-treatment with N-acetyl cysteine (a ROS scavenger) significantly inhibited leptin-induced NLRP3 and ASC overexpression, as well as IL-1β and caspase-1 activation (Ref. 24). Furthermore, pre-treatment of MCF-7 cells with tamoxifen (a selective oestrogen receptor modulator) or siRNA against ERα significantly decreased leptin-induced ROS, IL-1β maturation, caspase-1 production, as well as ASC speck formation and returned growth to almost normal levels (Ref. 24). On the other hand, treating MCF-7 cells with oestradiol increased leptin-induced growth and IL-1β maturation (Ref. 24). NADPH oxidase (NOX) is a membrane-bound enzyme that is responsible for the production of ROS in response to specific physiological stimuli (Ref. 232). NOX is an enzyme complex composed of multiple subunits. In MCF-7 BC cells, NOX1 and NOX2 subunits are mainly expressed (Ref. 233) where leptin was found to induce NOX activation. Nonetheless, pretreatment with diphenyleneiodonium (a pharmacological NOX inhibitor) inhibited leptin-induced ROS production and reduced leptin-induced increase in NLRP3, caspase 1 activation, ASC expression and speck formation (Ref. 24). Notably, leptin did not cause a remarkable change on NOX2 expression; however, it dramatically increased NOX1 mRNA and protein expression in a time- and dose-dependent manner (Ref. 24). Adding to that, NOX1 knockdown prevented leptin-induced ROS production and suppressed IL-1β maturation in MCF-7 BC cells. In addition, gene silencing of ERα markedly abolished leptin-induced NOX1 expression (Ref. 24). Moreover, oestradiol treatment increased NOX1 expression in MCF 7 cells (Ref. 24) (Fig. 5).

The ER-deficient MDA-MB231 BC and SK-BR-2 cells treated with leptin showed no significant effects on NLRP3, ASC or IL-1β protein expression (Ref. 24). MDA-MB231 BC cells treated with leptin showed non-significant changes in ROS generation or in IL-1β maturation. In addition, the ER-negative SK-BR-3 cells treated with leptin showed no significant effects on NLRP3 protein expression or on ASC protein expression (Ref. 24). Collectively, this proves that ER plays a pivotal role in ROS and inflammasome activation induced by leptin in BC cells.

Impact of leptin-induced NLRP3 activation on apoptosis and cell cycle progression in breast cancer

In BC, leptin increased the number of viable cells, suppressed caspase-7 and pro-apoptotic Bcl-2 associated X-protein (BAX), and increased expression of anti-apoptotic B cell lymphoma 2 (Bcl2) (Ref. 24). Thus, it collectively inhibited apoptosis. Furthermore, it induced the expression of cyclin D1 and enhanced cell cycle progression (Ref. 24). In BC cells, addition of selective NLRP3 inhibitor or transfection with siRNA against NLRP3 prevented the leptin stimulated tumour growth, restored caspase 7, abolished suppression of BAX and prevented leptin-induced Bcl2 expression. In addition, it also significantly decreased the populations of cells in S and G2-M phase and enhanced cell populations in G0–G1 phase of cell cycle and significantly reduced leptin-induced cyclin D1 expression (Ref. 24).

Leptin-induced inflammasome activation via ROS in vivo

Similarly, in MCF-7 tumour xenograft mice, treatment with leptin led to increased tumour growth, volume, size and weight (Ref. 24). Leptin also led to increased IL-1β, Bcl2 and cyclin D1 expression, and finally decreased the expression of BAX. Furthermore, treatment with tamoxifen prevented leptin-induced IL-1β, caspase 1 maturation, as well as ASC and NLRP3 inflammasome expression (Ref. 24). Moreover, in xenograft model, co-administration of Ac-YVAD-CMK; a capasase-1 inhibitor, with leptin has remarkably decreased leptin-induced tumour growth, IL-1β maturation, Bcl2 and cyclin D1 expression, and significantly restored BAX expression (Ref. 24). Collectively, *in vivo* and *in vitro* observations showed that obesity increases plasma levels of leptin that transactivates ER receptor leading to activation of NOX, increase in NOX1 expression and ROS generation leading to activation of inflammasome, tumour growth via modulating apoptosis and cell cycle progression (Ref. 24).

Wrap-up and insights

It would be beneficial to dig for the exact mechanism by which NLRP3 inflammasome affected the expression of apoptosis-related genes. Inflammasome activation subsequently led to IL-1β maturation and secretion, increased tumour growth and

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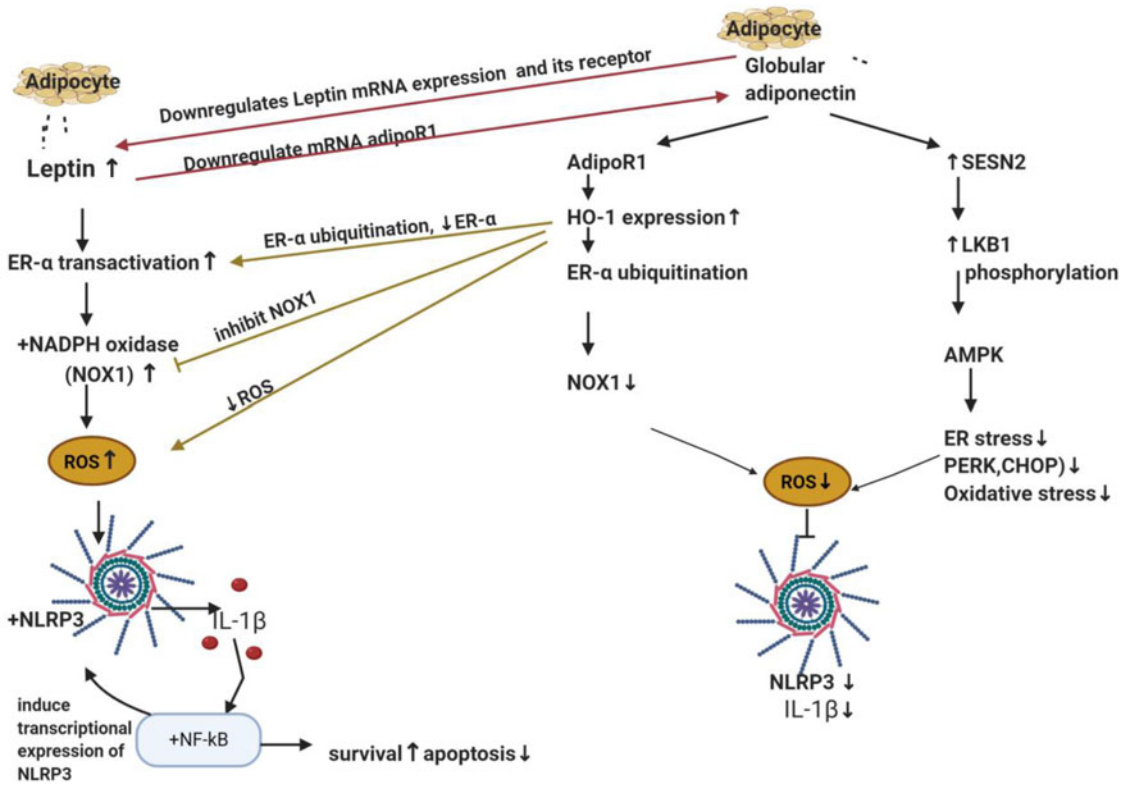

Figure 5. The antagonising effects of leptin and adiponectin on inflammasome in breast cancer. Leptin and adiponectin are adipokines (cytokines) secreted from adipocyte. Leptin transactivates ER-α and activates NADPH oxidase specifically NOX1 which is responsible for ROS production which then activates NLRP3 and IL-1β maturation. The latter activates NF-κB that regulates NLRP3 transcription. Globular adiponectin produces inhibitory actions on NLRP3 and ROS via two mechanisms. The first one through activation of its receptor (AdipoR1), elevation of the anti-oxidant 'HO-1'and downregulation of ER-α protein expression via ubiquitination and finally lowering the levels of NOX1. The second mechanism is SESN2/LKB1 upregulation and AMPK phosphorylation. It also decreases ER stress markers PERK, its downstream EIF2α and CHOP expression levels. It is worth mentioning that adiponectin and leptin antagonise each other on the transcription level of their receptors; adiponectin suppressed mRNA of leptin's receptor whereas leptin also suppressed adipoR1 mRNA expression in BC. ER-α, oestrogen receptor-α; NOX1, NADPH oxidase 1; ROS, reactive oxygen species; NLRP3, NOD-like receptor (NLR) family; pyrin domain-containing protein 3; IL-1β, interleukin-1β; NF-κB, nuclear factor κ B cells; AdipoR1, adiponectin receptor 1; HO-1, haeme oxygenase 1; SESN2, sestrine2; LKB1, liver kinase B1; AMPK, AMP-activated protein kinase; ER stress, endoplasmic reticulum stress; PERK, protein kinase RNA-like endoplasmic reticulum kinase; CHOP, C/EBP homologous protein.

decreased apoptosis (Ref. 24). Literature stated that IL-1β activated NF-κB pathway (Ref. 234) that increased survival and decreased apoptosis (Ref. 157). Recent studies showed that NLRP3 expression can be regulated at the transcriptional level through NF-κB-dependent pathway (Ref. 235) (Fig. 5). From all of the above-mentioned, it would be worth investigating the inflammasome/NF-κB pathway in BC and clarifying the exact mechanism of modulating the expression of apoptosis-related genes.

It has been stated that leptin-induced production of TNF-α (Refs 220, 221) and TNF-α induced an increase in extracellular ATP (Ref. 23), which in turn, activated purinergic receptors and led to invasion and metastasis via inflammasome activation (check purinergic part). In addition, literature reported that TNF-α was able to stabilise PD-L1 contributing to immunosuppression (Ref. 201). TNF-α blockade synergised with anti-PD-1 (Ref. 202). Therefore, it is promising to investigate the effects of leptin/TNF-α release and its correlation with PD-L1 immunosuppression. Blocking this pathway in obese ER-positive BC patients might give a promising synergistic effect in combination with anti-PD-1 or anti-PD-L1 immunotherapy. In addition, further investigation of the effect of leptin-induced ATP release and the subsequent purinergic/inflammasome activation, as well as its effect on MMP and VEGFA in BC cells is interesting; since this pathway might highlight targets that might counteract invasion and angiogenesis in BC. Furthermore, leptin showed pro-tumour effects and LDFI (a leptin antagonist) markedly decreased tumour growth in xenograft models, thus LDFI might be very beneficial to investigate its effect if used in combination with chemotherapy, especially in obese patients (Ref. 236). Literature reported that leptin directly stimulated IL-18 expression and promoted migration and invasion of BC cells. Surprisingly, these effects were abolished by the co-incubation of Bay11-7082 (a pharmacological NF-κB inhibitor) (Ref. 76). Since IL-18 induced PD-1 expression in BC (Refs 198, 199), it would be worth to investigate the effect of combining Bay11-7082 and leptin on inflammasome/PD-1 expression and whether Bay11-7082 would give a synergistic effect if co-administered with anti-PD-1.

Globular adiponectin

Adiponectin exists as a full-length protein of 30 kDa (Ref. 237). It is the most abundant adipokine in the circulation where it accounts for approximately 0.01% of total plasma proteins (Refs 238, 239). Adiponectin's anticancer activities are mediated through different mechanisms including cell cycle arrest, induction of apoptosis and inhibition of migration/invasion of cancer (Refs 240, 241, 242). In addition to the full-length form, globular adiponectin can be generated through proteolytic cleavage, which is a fragment containing the globular domain of adiponectin. Despite the low circulating concentration of globular adiponectin, it possessed potent diverse physiological activities and inhibited LPS primed inflammasomes activation through autophagy induction and AMPK signalling in macrophages (Refs 243, 244, 245)

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Globular adiponectin opposed leptin-induced NLRP3 inflammasome activation and breast cancer growth

In MCF-7 BC cells, globular adiponectin showed suppressive effects on inflammasomes activation, where it significantly decreased the levels of IL-1β, caspase 1, NLRP3, ASC speck formation and ASC (Refs 227, 246). Similarly, globular adiponectin opposed leptin-induced growth of cancer cells and inhibited the leptin-induced NLRP3 inflammasome activation and suppressed the elevated ASC, caspase-1 and IL-1β. Furthermore, it suppressed leptin viability, restored cell cycle and apoptosis to normal levels (Refs 227, 246).

Globular adiponectin antagonises leptin-induced breast cancer growth via ER-α ubiquitination and HO-1 induction

A pre-proof literature reported that globular adiponectin exerted its inhibitory action on leptin-induced inflammasome activation via upregulation of haeme oxygenase-1 (HO-1) in a dose- and time-dependent manner (Ref. 246); which has been reported to exhibit anti-oxidant activities that reduced ROS (Ref. 247). Moreover, addition of SnPP (a pharmacological inhibitor of HO-1) or siRNA HO-1 abrogated the suppressive effects of globular adiponectin on NLRP3 and ASC (Ref. 246). The biological effects of adiponectin are initiated by binding with its specific transmembrane receptors; adipoR1 or adipoR2 (Ref. 248). In MCF-7 BC cells, SiRNAs of adipoR1 or adipoR2 significantly inhibited the upregulation of HO-1 expression and abolished the suppressive effects of globular adiponectin on inflammasome. Notably, adipoR1 SiRNAs showed higher preventative effect (Ref. 246). Furthermore, globular adiponectin significantly attenuated leptin-induced ROS and NOX activation (Ref. 246). All these effects were abolished with SnPP or gene silencing of HO-1. Interestingly, globular adiponectin markedly downregulated transcriptional activity of ER-α receptor which was enhanced by leptin. Moreover, results showed that globular adiponectin significantly downregulated protein expression of ER-α receptor through increasing ER-α ubiquitination (this explains why it affected its protein level and not its mRNA) (Ref. 246) (Fig. 5). Similar to *in vitro* effects, globular adiponectin inhibited NLRP3, ASC, enhanced apoptosis, decreased Ki67 and decreased tumour volume *in vivo* (Ref. 246).

Globular adiponectin decreased ER stress markers and viability of ER-positive breast cancer cells via suppression of inflammasomes through SESN2/AMPK/ER stress signalling pathway

Accumulation of unfolded proteins in the ER lumen, occurring during ER stress, is sensed by protein kinase RNA-like endoplasmic reticulum kinase (PERK) that induces the activation of unfolded protein response pathways and phosphorylates its downstream eukaryotic initiation factor 2 alpha (eIF2α) (Refs 249, 250, 251). In addition, it subsequently activates the transcription factor C/EBP homologous protein (CHOP); a marker for ER stress that propagates ROS signals, contributing to apoptosis (Refs 249, 250, 251). Sestrine 2 (SESN2) is known to provide cytoprotection against ER stress and reduces levels of cellular ROS (Ref. 252). It is one of the critical regulators of 5′ AMP-activated protein kinase (AMPK) activation and was found to decrease ROS and oxidative stress (Ref. 252) via its upstream liver kinase B1 (LKB1), that functions as a tumour suppressor gene (Refs 253, 254). Literature reported that LKB1/AMPK boosted Nrf2 and increased HO-1 expression that further decreased ROS and oxidative stress (Ref. 255).

Globular adiponectin decreased ER stress markers PERK, its downstream EIF2α and CHOP expression levels (Ref. 227) (Fig. 5). Addition of the classical ER stress inhibitor (TUDCA) resulted in a significantly reduced level of mature IL-1β and caspase 1 in a dose-dependent manner (Ref. 227). On the contrary, addition of the pharmacological ER stress inducer tunicamycin markedly increased mature IL-1β and caspase 1 in MCF-7 BC cells (Ref. 227). Globular adiponectin treatment induced a marked increase in protein expression of SESN2 and phosphorylation of AMPK and increased complex formation of SESN2/AMPK and SESN2/LKB1 in MCF-7 BC cells (Ref. 227). Results showed that SESN2 acted as a scaffold for AMPK and LKB-1 (Ref. 227). Treatment with compound C (pharmacological inhibitor of AMPK) or gene silencing of AMPKα and SESN2 abolished the inhibitory effects of globular adiponectin on NLRP3 inflammasome (Ref. 227) and restored the ER stress markers (PERK, EIF2 and CHOP). In addition, in MCF-7 cells, transfection with SESN2 siRNA inhibited the globular adiponectin-mediated AMPK phosphorylation and completely abolished LKB1/AMPK complex formation (Ref. 227). In ER-positive cells (MCF-7 or T47D), inflammasome activation was observed to contribute to their growth, but not in ER-negative MDA-MB231 cells (Refs 24, 227). Similarly, pharmacological inhibitors of inflammasome (Ac-YVAD-cmk, MCC950 and interleukin 1 receptor antagonist 'IL-1Ra') or globular adiponectin significantly decreased the cell viability of MCF-7 and T47D cells but not MDA-MB231 and upregulated the negative modulators of cell cycle: $P27^{kip}$ and P53, downregulated cyclin D1 and induced cell cycle arrest at G0/G1 phase (Ref. 227).

In MCF-7, tumour xenograft model established in BALB/c nude mice globular adiponectin, inhibitor of NLRP3 (MCC950) or IL-1Ra, inhibited tumour growth (Ref. 227), suppressed markers of cell proliferation including Ki67 and cyclin D1, increased the expression of $p27^{kip1}$ and enhanced apoptosis (Ref. 227). In addition, globular adiponectin decreased the expression levels of inflammasome components, increased phosphorylation of AMPK, expression of SESN2 but decreased CHOP expression (Ref. 227). All of the above results revealed that adiponectin decreased the growth of BC cells via suppression of inflammasomes through SESN2/AMPK/ER stress signalling pathway (Fig. 5).

Wrap-up and insights

Globular adiponectin was shown to decrease ER stress, inhibit inflammasome activation in BC cells (Ref. 227) and exert antitumour activities (Refs 227, 228), and low plasma levels of adiponectin have been linked to increased risk of certain types of cancers (Refs 224, 225). In addition, a recent study stated that globular adiponectin exerted its inhibitory effect through AdipoR1 (Ref. 246). It is also worth mentioning that AdipoRon (AdipoR agonist that binds to AdipoR1 and AdipoR2) induced apoptosis and decreased proliferation in human ovarian cancer cells; in addition, it inhibited the proliferation of myeloma cells and human osteosarcoma (Refs 256, 257, 258). Therefore, it would be beneficial to investigate the effect of AdipoRon in ER + BC patients and can be investigated further to be used in combination with chemotherapy as it might be a promising drug that decreases BC growth especially in obese patients.

Interestingly, it has been reported that leptin induced production of TNF-α (Refs 220, 221) that led to stabilisation of PD-L1. Literature reported the antagonising effect of adiponectin on leptin mRNA and receptor (Ref. 223). Therefore, AdipoRon's effect on PD-1 and PD-L1 expression should be investigated.

Molecular pathways relating globular adiponectin and leptin in BC should be investigated. It has been noticed that leptin activated NLRP3 inflammasome causing increased BC growth via ER-α activation (Ref. 24). On the contrary, globular adiponectin enhanced HO-1 expression and SESN2/LKB1/AMPK complex formation (Refs 227, 246). Literature reported that AMPK activated Nrf2 that increased the expression of HO-1 (Ref. 255).

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This might explain how globular adiponectin enhanced HO-1 expression and subsequently inhibited inflammasome (since the exact mechanism in cancer cells was unclear) (Ref. 246). From all the above-mentioned, the effect of adiponectin-induced AMPK/nrf2/HO-1/ER-α ubiquitination and suppression of leptin-induced inflammasome activation and BC growth should be further investigated.

Non-coding RNA and inflammasomes in breast cancer

Initially, non-coding RNAs (ncRNAs) were viewed as 'transcriptional noise' (Ref. 259). Later on, studies showed that ncRNAs are regulators of crucial biological processes such as cell proliferation, differentiation and invasion (Refs 260, 261). According to their length, ncRNAs are divided into long non-coding RNAs (lncRNAs) and short non-coding RNAs (Ref. 259). The latter comprises small interfering RNAs, small nucleolar RNAs, microRNAs (miRNAs) and PIWI-interacting RNAs (Ref. 259). miRNA and lncRNA represent the most-studied family classes and their deregulation was correlated with BC (Ref. 260).

MiRNA and inflammasomes in breast cancer

MiRNAs are 17–25 nucleotides in length and can function as tumour suppressor miRNAs or as oncogenes (oncomiRs) (Ref. 262). For instance, in the aggressive TNBC, miR-21 and miR-221 significantly overexpressed while miR-205, miR-145 and miR-122a were downregulated (Ref. 263). In addition, miRNA-107 was associated with BC progression (Ref. 264).

MiRNA-223 has been shown to dampen neutrophilic inflammation via NF-κB suppression (Ref. 265). In BC, the only investigated miRNA inhibiting inflammasomes, till date, is miR 223-3p. Intended overexpression of miR-223-3p in human BC cells attenuated the NLRP3 over-expression (wild type), decreased protein expression levels of ASC, IL-1β and IL-18 (Ref. 25), while increased protein expression of IL-10 (Ref. 25). Furthermore, it lowered tumour volume, increased survival and apoptotic rate. In addition, it decreased the number of ki67 and VEGF-positive cells compared to negative control group. Snail gene is a well-known inducer of EMT and has been associated with BC poor prognosis and metastasis via increasing the expression of MMP-9 (Ref. 266). In the light of the fact that NLRP3 showed opposing impacts in cancer (Ref. 267), a recent study in August 2022 showed that overexpression of snail-regulated miRNA-21 significantly suppressed cisplatin-induced NLRRP3 activation of TAMs leading to chemo-resistance in murine 4T1 BC cells. In addition, miR-21 has been shown to suppress PTEN causing NLRP3 inactivation (Ref. 267).

LncRNA and inflammasomes in breast cancer

LncRNAs are more than 200 nucleotides in length and their dysregulation was associated with BC (Ref. 268), for example, the lncRNA BCRT1 was significantly upregulated in BC tissues and was correlated with BC poor prognosis (Ref. 269). A recent study provided a theoretical reference and reported eight pyroptosis-related lncRNAs in BC model including AC004585.1, DLGAP1-AS1, TNFRSF14-AS1, AL606834.2, Z68871.1, AC009119.1, LINC01871 and AL136368.1. Furthermore, mRNAs of AIM2, CASP1, CASP4, IL-18 and NLRP1 were co-expressed with AL606834.2, AC004585.1 and LINC01871 (Ref. 268). The aforesaid lncRNAs require practical investigation.

A wrap-up and insights

It would be very beneficial to investigate the effect of combining miR-223-3p synthetic nucleotides with chemotherapy in BC cells (luminal B) that have high ki67, since miR-223-3p inhibited NLRP3 and decreased the expression of ki67 and proliferation (Ref. 25). In addition, miR223-3p might give a synergistic effect if used with sorafenib, since it decreased the expression of VEGF in BC (Ref. 25). Literature showed that IL-18 caused immunosuppression by inducing PD-1 expression in cancer (Ref. 270), and since miR223-3p overexpression decreased IL-18 (Ref. 25), then it might be a promising adjuvant with anti-PD-1/PD-L1 blockade immunotherapy ameliorating immunotherapy resistance in BC. Moreover, further investigation

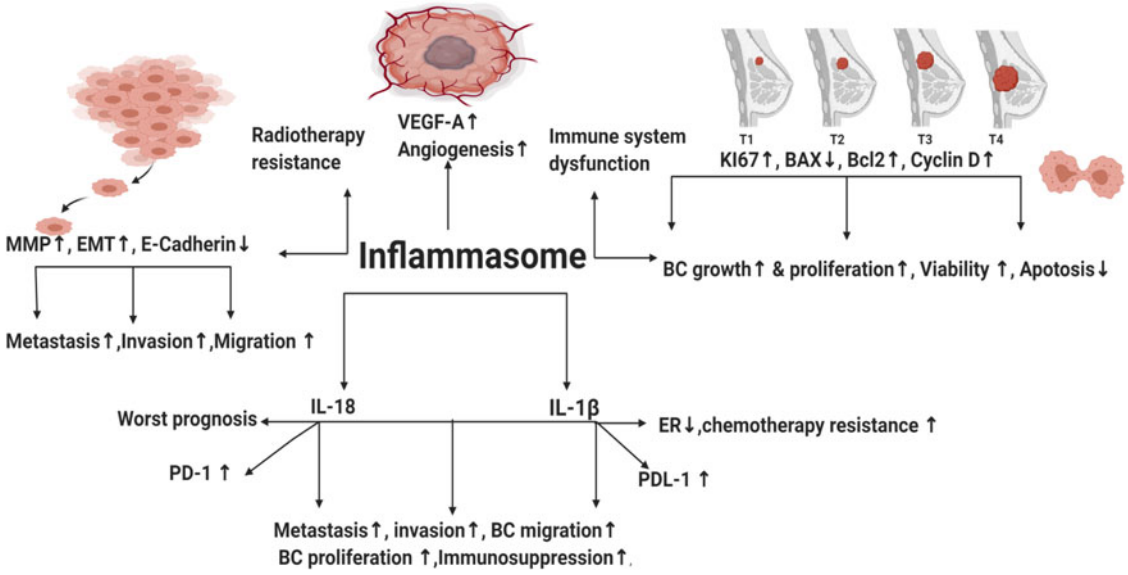

Figure 6. Tumour-promoting effects of inflammasomes in BC. Inflammasomes contributed to therapy failure in BC since it enhanced radiotherapy, chemotherapy and immunotherapy resistance. It led to immune system dysfunction and increased expression of PD-1/PD-L1. In addition, it enhanced cell cycle progression, BC growth and viability through increasing Cyclin D, KI67 and anti-apoptotic BCl2 while lowering pro-apoptotic BAX. Invasion and angiogenic markers such as MMP, EMT and VEGF-A were increased by inflammasomes leading to BC metastasis, invasion and angiogenesis, respectively. Thus, collectively inflammasomes inhibition is a promising multi-strike in BC. IL-1β, interleukin-1β; IL-18, interleukin 18; MMP, matrix metalloproteinases; VEGF-A, vascular endothelial growth factor A; EMT, epithelial mesenchymal transition; ER, oestrogen receptor; BC, breast cancer; KI67, proliferative index; BAX, Bcl-2 associated X-protein; Bcl2, B-cell lymphoma 2.

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should be done on ADAMTS9-AS2's effect on miR-223-3p in BC. Most importantly, more miRNAs targeting inflammasome should be investigated in BC, for example, miR-144 that has been extensively studied and was reported to regulate BC invasion, migration and proliferation (Refs 271, 272). In addition, it was involved in the regulation of radiotherapy sensitivity (Ref. 273). Thus, miR-144 is a worth examining candidate to unravel if it can impact inflammasome pathway in BC cells and correlate its expression with ATP/purinergic receptors, especially in ER-positive BC cells.

In a recent study reported by Ren *et al.* (Ref. 274), lncRNA ADAMTS9-AS2 sponged and inhibited miR-223-3p leading to increased NLRP3 expression and triggered pyroptotic cell death in cisplatin-treated gastric cancer cells. These effects were reversed by miR-223-3p overexpression (Ref. 274). LncRNA XIST has been extensively studied by our research group (Refs 275, 276). LncRNA XIST acted as a tumour suppressor where it was downregulated in BC tissues (Ref. 275) and was able to suppress PD-L1 expression in MDA-MB231 cells (Refs 275, 276). In addition, PD-L1-overexpressing BC patients as well as TNBC cell lines showed an inverse correlation with low levels of XIST, where XIST was described as non-invasive cancer immune biomarker for anti-PD-L1 personalised therapy (Ref. 276). Surprisingly, downregulation of lncRNA XIST activated NLRP3 inflammasome and increased caspase1, IL-1β and IL-18 in lung cancer cells (Ref. 277). Furthermore, overexpression of lncRNA GAS5 induced a time-dependent activation of ASC, caspase-1 and IL-1β in ovarian cancer (Ref. 278). In mouse macrophages, the lncRNA NEAT1 promoted pyroptosis and enhanced assembly of several inflammasomes (NLRP3, NLRC4 and AIM2) and subsequently increased caspase 1 and IL-1β (Ref. 279). Another study reported that NEAT1 increased the expression of NLRP3 via targeting miR3076-3p (Ref. 280). Moreover, knockdown of lncRNA Gm4419 ameliorated inflammation in diabetic nephropathy through NF-κB/NLRP3 inflammasome (Ref. 281). In addition, Gm4419 led to an increase in the transcription of TNF-α, IL-1β and IL-6 through NF-κB (Ref. 282). Thus collectively, it would be worth investigating the effects of the above-mentioned lncRNAs on inflammasomes in BC, and its correlation with BC progression and immunotherapy resistance.

Conclusion

In spite of dramatic advances in BC diagnosis, personalised treatments and recently approving immunotherapy against aggressive BC unfortunately, therapy failure occurs in many BC patients because of resistance, tumour recurrence and serious side effects. Unluckily, many BC patients were obliged to discontinue the newly approved immunotherapy treatment due to serious irAE and low response rates. There is an urge to dig for new molecular targets to lessen these obstacles and improve overall therapy response. In this review, we have hoped to shed the light on the inflammasome pathway in BC as it might unravel the hidden molecular contributors to therapy failure, tumour progression and immune dysfunction. Additionally, this review highlights several novel molecules targeting the inflammasome pathway, thereby ameliorating tumour progression, therapy resistance and potentiating the effect of immunotherapy that is recently approved in the treatment of BC. It has been shown throughout numerous studies that inflammasomes and the subsequent IL-1β and IL-18 enhanced invasion, metastasis and angiogenesis. Second, it increased proliferation, decreased apoptosis and increased viability of BC, thereby promoted tumour progression and therapy resistance. Additionally, inflammasomes led to immune system dysfunction, increased PD-L1 and PD-1 expression in BC. Figure 6 summarises the tumour-promoting effects of inflammasomes in BC. Finally, there is an urge to target inflammasome pathway in clinical trials against BC, since studies showed that counteracting this pathway synergised PD-L1 blockade, decreased chemotherapy resistance, angiogenesis and tumour growth of BC. Altogether, inflammasome targeting is a promising molecular multi-strike that might win the battle against BC.

Competing interest. None.

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