Immune system, inflammatory response, and regulated cell death in breast cancer research (Review)

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Abstract. Breast cancer (BC) ranks among the most prevalent malignant tumors in female patients. It represents a longstanding challenge to medical professionals in terms of diagnosis and treatment. Exploring BC pathogenesis offers insight into its complexity and facilitates the exploration of more effective treatment strategies. The present review aimed to describe the involvement of the immune system, inflammatory response and regulated cell death in BC development, offering avenues for novel therapeutic strategies against BC. Identifying novel treatment methods is key for enhancing the prognosis of patients with BC.

Contents

1. Introduction

Breast cancer (BC) is among the most common cancers in female patients globally. It has seen rising prevalence and mortality rates, representing a challenge to both the medical ERcommunity and society (1). The etiology of BC involves a complex interplay of modifiable and non-modifiable factors, which include genetic susceptibility, environmental exposure, hormone levels, nutritional status and lifestyle choices (2).

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Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; AMPK, AMP-activated protein kinase; BC, breast cancer; Bim, Bcl-2-interacting mediator of cell death; BMI, body mass index; CAF, cancer-associated fibroblast; CRISPR/Cas9, clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9; CTLA-4, cytotoxic T lymphocyte-associated protein 4; DC, dendritic cell; EBV, Epstein-Barr virus; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; FasL, Fas ligand; GLD, generalized lymphopro-liferative disease; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSDM, gasdermin; HCMV, human cytomegalovirus; HIF, hypoxia-inducible factor; HLA-A2, human leukocyte antigen-A2; HMGB1, high mobility group box 1; HPV, human papillomavirus; HR, hazard ratio; ICI, immune checkpoint inhibitor; IGF-1, insulin-like growth factor 1; ILC, innate lymphoid cell; IRAK, interleukin-1 receptor-associated kinase; LAG-3, lymphocyte activation gene 3; LPR, lymphoproliferation; MHC, major histocompatibility complex; OS, overall survival; PCD, programmed cell death; PD-L1, programmed death-ligand 1; PRR, pattern recognition receptor; RCD, regulated cell death; SMAC/DIABLO, second mitochondria-derived activator of caspase/direct IAP-binding protein with low pI; TAM, tumor-associated macrophage; TLS, tertiary lymphoid structure; TME, tumor microenvironment

Key words: breast cancer, immune system, inflammatory response, regulated cell death, therapy

Notable risk factors for BC include personal or positive family history of BC, obesity, tall height, smoking, alcohol consumption, early menarche, late menopause, sedentary lifestyle, nulliparity and hormone replacement therapy (3). Factors associated with a decreased risk of BC include high parity, breastfeeding, regular physical activity and weight management. Increases in BC incidence are attributed to rising obesity rates and declining fertility (4,5). BC in female patients is the second most common cancer globally according to the Global Cancer Observatory Database 2022 (6), with an estimated 2.3 million new cases accounting for 11.6% of all cancer cases. It is the fourth leading cause of cancer-associated death worldwide, resulting in ~666,000 deaths, which constitute 6.9% of all cancer deaths in 2022 (6). This presents significant challenges to public health and healthcare systems.

BC is a complex disease with diverse molecular subtypes and outcomes (7). Cytokines exhibit a dual role in cancer as they can have both pro- and antitumor effects (8). In terms of modulating immune cells, cytokines exhibit both pro- (stimulating immune responses) and anti-inflammatory (suppressing immune responses) properties, thereby serving a complex role in the tumor microenvironment (TME) (9,10). Chronic inflammation and the inflammatory milieu are associated with higher BC incidence rates (11).

The development and homeostasis of multicellular organisms rely on regulated cell proliferation and proper disposal of unnecessary or potentially harmful cells. Inflammation is a biological response of the immune system triggered by viruses, toxic compounds and other factors (12). Cell damage and infection activate the immune system, resulting in inflammation, regulated cell death (RCD) and regeneration of inflammatory cells (13).

Programmed cell death (PCD) was first used to describe a form of cell death actively driven by endogenous genetic programs during individual development and tissue homeostasis maintenance, such as classical apoptosis (14). PCD typically does not trigger an inflammatory response and is morphologically characterized by cell shrinkage, chromatin condensation and preservation of membrane integrity (15). Subsequent studies have found that, in addition to PCD, numerous cell death events do not result from external mechanical damage, but occur depending on the activation or inhibition of specific signaling pathways (16,17). Therefore, the broader concept of RCD was proposed. RCD not only includes apoptosis, but also involves necroptosis, pyroptosis and ferroptosis. These death modes differ in terms of morphology, immunological effects and inflammatory responses, but collectively reflect the regulation of cell death. PCD can be regarded as a physiological and evolutionarily conserved type of RCD, while RCD reveals the dynamic characteristics of cells regulated through molecular mechanisms to affect immune responses, inflammation and disease progression under pathological stress and microenvironmental changes (18).

Membrane-bound and cytoplasmic proteins participate in RCD, forming a complex cascade through transcriptional changes and post-translational protein modifications that induce cell death (19).

Necrotic material activates the immune system and is promptly phagocytosed and degraded by both macrophages and neutrophils, efficiently eliminating necrotic cell debris (20,21). The dissolution of infected or damaged cells constitutes the primary strategy for eliminating pathogens and preserving health. This process ensures the replenishment of normal cells in the body and sustains tissue homeostasis (22). Inflammation becomes problematic when harmful stimuli cannot be eliminated through RCD (23). Certain scholars believe that RCD compromises host defense mechanisms against intracellular pathogens, while others propose that cell bodies resulting from RCD modulate the innate immune response to facilitate infection clearance under appropriate immunological and microenvironmental conditions (24,25).

The present review aimed to explore the interplay among the immune system, inflammatory response and RCD in BC, seeking novel therapeutic targets and approaches at the molecular level (Fig. 1).

2. Importance of the immune system in BC development and progression

Microbial and viral infections represent threats to human health. The immune system has evolved complex mechanisms to recognize and eliminate pathogens, thereby safeguarding the host from disease. Human immune response comprises innate and adaptive immunity (26).

Innate immune system. The innate immune system serves as the primary defense mechanism and initiates the rapid response (27). This system includes physical barriers such as the skin and mucous membranes, as well as cellular components, such as phagocytes and natural killer (NK) and dendritic cells (DCs) (28). Innate immune cells undergo phenotypical and functional maturation upon encountering pathogens, leading to the production of highly efficient antigen-presenting cells that bridge innate and adaptive immunity (29).

The innate immune system serves a key role in eradicating nascent tumor cells during the clearance phase of cancer immunoediting. NK cells recognize stress ligands, such as major histocompatibility complex (MHC) class I polypeptide-related sequence A/B and poliovirus receptor, on the surface of tumor cells through their activating receptors natural killer group 2 member D (NKG2D) and DNAX accessory molecule-1 (DNAM-1), and induce tumor cell apoptosis by releasing perforin and granzyme B (30-33). IFN-γ secreted by NK cells inhibits angiogenesis and activates macrophages (34). However, the TME reprograms myeloid cells during the equilibrium and escape stages, leading to notable immunosuppressive cell infiltration. Tumor-associated macrophages (TAMs) are one of the most abundant types of immune cell with high plasticity in the TME. They exhibit an M1-like phenotype, secreting pro-inflammatory factors and exerting antitumor effects. However, they are more commonly polarized into an M2-like phenotype in most solid tumors, releasing factors such as IL-10, transforming growth factor (TGF)-β and VEGF, that promote angiogenesis, tissue remodeling and tumor metastasis, while suppressing T cell-mediated immune responses. Therefore, TAMs serve a key role in tumor progression and immune escape and are important targets for current immunotherapy interventions (35).

The innate immune system responds promptly via macrophages and neutrophils phagocytosing pathogens and sending

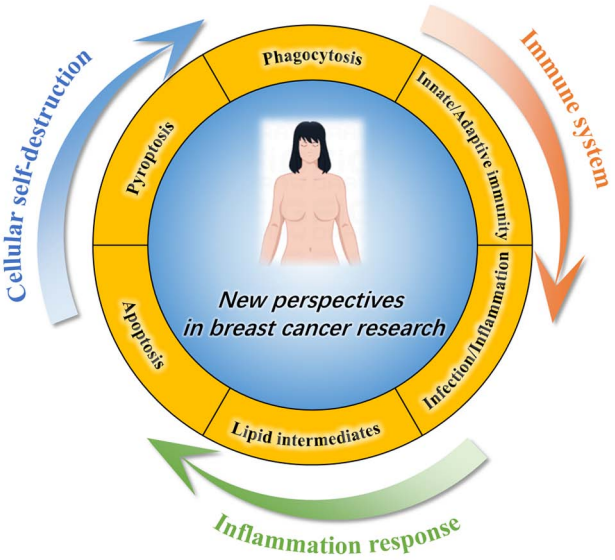

Figure 1. Immune system, inflammatory response and regulated cell death in breast cancer research.

inflammatory signals that initiate DC recruitment (36,37). Pattern recognition receptors (PRRs) enable innate immune cells to detect two types of danger signals: Pathogen-associated molecular patterns from microbial infection and danger-associated molecular patterns (DAMPs) from dying or damaged cells. PRRs include toll-like receptors (TLRs), C-type lectin receptors, retinoic acid-inducible gene-I (RIG-1)-like receptors and nucleotide-binding oligomerization domain-like receptors (NLRs), which recognize these signals and activate immune responses (38).

Immune cells eliminate pathogens upon activation via cytokine and chemokine secretion, as well as phagocytosis. Cytokines, such as IL-1, IL-6, tumor necrosis factor (TNF-α) and IFN, initiate signaling pathways. For example, IL-1 and TNF-α are involved in the activation of the NF-κB pathway, while IFN stimulates the JAK/STAT pathway to induce an antiviral state mediated by IFN-stimulated genes (39,40). Cytokines in the TME construct a complex signaling network with a context-dependent function. Type I IFN is a core coordinating factor in antitumor immunity. It directly inhibits tumor cell proliferation via the JAK1/tyrosine kinase 2-mediated STAT1/STAT2/interferon regulatory factor 9 (IRF9) signaling complex (41), while upregulating MHC-I molecule expression, promoting DC maturation (42) and enhancing the survival and effector functions of $CD8^+$ T cells (43).

The inflammasome is a molecular platform of innate immunity that responds to cell stress and infection. The NLRP3 inflammasome senses multiple upstream signals [ion flux, reactive oxygen species (ROS) and lysosomal damage] and forms a complex that activates caspase-1 (44). Activated caspase-1 serves two key functions: Processing pro-IL-1β and pro-IL-18 into their mature cytokine forms (45) and cleaving gasdermin D (GSDMD) to release its N-terminal fragment, which oligomerizes in the plasma membrane to form pores and induce pyroptosis (46).

Inflammasome signaling in BC has context-dependent effects. NLRP3 activation within tumor cells in estrogen receptor-negative tumors, such as triple-negative BC (TNBC), promotes pre-metastatic niche formation and distant metastasis through IL-1β autocrine/paracrine loops (47). By contrast, inflammasome activation in hematopoietic cells enhances antitumor immunity, where pyroptosis releases tumor antigens, which facilitate DC priming and T cell activation (48). Histone deacetylase inhibitors in TNBC can switch caspase-3 activity from apoptosis toward pyroptosis by cleaving GSDME (49). This causes tumor cell lysis and DAMP release, which recruit $CD11b^+$ myeloid cells, enhance antigen presentation and increase $CD8^+$ T cell infiltration and granzyme B secretion, restoring antitumor immunity (50). Conversely, silencing or loss of pyroptotic effectors, such as GSDME, during tumor progression allows BC cells to maintain a 'cold tumor' state, characterized by low immune cell infiltration and weak immune activation, and escape immune surveillance (51).

Adaptive immune system. The adaptive immune system mediates antigen-specific responses through specific T and B cell receptors, forming long-lasting immune memory. It serves as the core force for eliminating tumor cells (52-54). The efficacy of the adaptive immune response in BC directly determines patient prognosis and immunotherapy response (55,56). Numerous types of conventional anticancer therapy, such as anthracyclines, oxaliplatin and radiotherapy, can induce immunogenic cell death, exposing tumor cells to calreticulin and releasing DAMPs such as ATP and high mobility group box 1 (HMGB1). These signals enhance the phagocytic, maturation and cross-presentation capabilities of DCs (57).

The core of the adaptive immune system antitumor effect lies in cellular immunity, particularly the recognition and killing of tumor neoantigens presented by tumor cells via MHC-I molecules by $CD8^+$ cytotoxic T lymphocytes (CTLs) (58). $CD4^+$ T helper (Th) cells regulate the function of CTLs and NK and antigen-presenting cells by secreting cytokines, such as IFN-γ and IL-2. They also provide assistance to B cells, coordinating the humoral immune response (59).

However, the TME of BC typically secretes factors, such as VEGF, IL-10 and TGF-β, to suppress DC maturation, thereby impeding T cell priming (60). Simultaneously, activated T cells are prone to exhaustion under sustained antigenic stimulation, manifesting as high expression of inhibitory receptors, such as PD-1, T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) and lymphocyte activation gene 3 (LAG-3), and gradually losing their effector function (61). BC cells actively induce T cell exhaustion by binding PD-1 through high programmed death-ligand 1 (PD-L1) expression, representing one of the primary adaptive immune escape mechanisms. Immune checkpoint inhibitors (ICIs) restore T cell function and enhance antitumor immune responses by blocking the PD-1/PD-L1 pathway (62).

Beyond antibody production, B cells participate in antigen presentation and cytokine secretion, forming tertiary lymphoid structures (TLSs) within tumor tissue. TLSs comprise T and B cells and DCs and sustain local antitumor immune responses. Their presence is typically associated with higher T cell infiltration, more active immune response and improved patient prognosis (63).

Adaptive immune pathways serve tumor-suppressing roles and drive immune escape in BC development and progression. The efficacy of cancer vaccines, adoptive cell therapy

and ICIs depends on the integrity of antigen presentation, T cell activation and effector function (64-66). CTLs become exhausted due to persistent antigen stimulation when DCs are blocked. Alternatively, tumor cells evade immune recognition by downregulating MHC-I and upregulating PD-L1. The adaptive immune response becomes difficult to sustain, allowing tumors to progress (67). The presence of B cells and TLSs enhances local immune responses, but their antitumor functions are typically weakened under the regulation of immunosuppressive cytokines, such as TGF-β and IL-10, and may shift toward pro-tumor effects (68). Therefore, immune escape in BC is the outcome of a prolonged 'arms race' between the adaptive immune system and the tumor. On one hand, the immune system shapes tumor evolution by recognizing and eliminating it (69). On the other hand, the tumor reciprocally reprograms the immune response through multiple mechanisms, such as secreting immunosuppressive cytokines (TGF-β and IL-10), inducing regulatory T cells, and upregulating immune checkpoint molecules such as PD-L1 (70,71). Future therapeutic strategies may simultaneously enhance adaptive immune effects and prevent TME suppression to disrupt this malignant equilibrium and achieve durable antitumor control.

3. Types of RCD

Apoptosis and autophagy. Continuous signal release during apoptosis attracts phagocytes and facilitates cell clearance (72). Granzyme family molecules released from activated T and NK cells induce apoptosis. These protein hydrolases target cysteine aspartyl proteases or BH3-interacting domain death agonist, activating them and bypassing upstream signaling, thus initiating target cell apoptosis (73). Tanzer *et al* (74) identified a specific secretome signature distinguishing apoptosis from other forms of cell death, where apoptotic cells predominantly release nucleosomal components. Saxena *et al* (64) discovered that apoptotic lymphocytes and macrophages release anti-inflammatory metabolites, maintaining plasma membrane integrity and inducing genetic programs promoting inflammation suppression, cell proliferation and wound healing.

Apoptosis is key for tissue development and renewal as it regulates cell population balance. Additionally, CTLs maintain tissue health by inducing apoptosis in target or virus-infected cells (75). Reports indicate that apoptosis is key in the adaptive immune system, contributing to the loss of auto- or non-reactive T cell receptor expression by thymocytes and the absence of auto-reactive immature B cells (76,77). Inflammation resolution involves the emergence of apoptotic neutrophils (78).

Apoptosis defects result in autoimmune abnormalities. Lymphoproliferation (LPR) and generalized lymphoproliferative disease (GLD) are natural mouse mutants associated with lymph node and spleen enlargement and the development of systemic lupus erythematosus-like autoimmune disorder (79). Functional defects in Fas and FasL genes result in LPR and GLD phenotypes (80). Patients with autoimmune lymphoproliferative syndrome carry mutations in somatic or germ cells encoding Fas or FasL genes. The Fas-mediated extrinsic apoptotic pathway clears peripheral T cells and eliminates self-reactive B cells. Studies have shown that Bcl-2-interacting mediator of cell death (Bim)-mediated apoptosis regulates short-lived myeloid cells, including eosinophils, neutrophils and monocytes (81,82). These findings highlight the key role of the Fas-FasL system and Bim-mediated endogenous and exogenous apoptotic pathways in autoimmune disease development (83).

In addition to exogenous stimuli, apoptosis is regulated or activated by internal stimuli, such as DNA damage and oxidative stress (84). The intrinsic pathway for this process is characterized by mitochondrial regulation and non-receptor-mediated initiation. Stimuli such as oxidative stress cause mitochondrial membrane disruption, leading to the formation of mitochondrial permeability transition pores, thereby allowing pro-apoptotic factors to enter the cytosol. This intrinsic apoptosis pathway involves key mediators, such as Bcl-2 family proteins, including pro-apoptotic Bax and anti-apoptotic Bcl-2 (85). These proteins regulate the release of cytochrome c from the mitochondria into the cytosol, where it forms a complex with apoptotic protease-activating factor 1 and procaspase-9, known as the apoptosome (86). This complex activates mTOR, which triggers executioner caspases such as caspase-3, -6 and -7, leading to apoptosis (87). Additionally, proteins, such as second mitochondria-derived activator of caspase/direct IAP-binding protein with low pI (SMAC/DIABLO) and apoptosis-inducing factor, participate in caspase-dependent and -independent pathways, respectively. SMAC/DIABLO inactivates apoptosis protein inhibitors, thus facilitating apoptosis, while apoptosis-inducing factor translocates to the nucleus once released from the mitochondria to induce DNA fragmentation and chromatin condensation (88).

Research indicates that the endoplasmic reticulum (ER) is also involved in apoptosis (89). Excess accumulation of proteins within the ER and disruption of calcium homeostasis trigger ER stress, leading to apoptosis (90). Caspase-12 is located on the ER membrane and is key for ER-mediated apoptosis (91). The ER response triggers caspase-12 expression while translocating cytosolic caspase-7 to the ER membrane, where caspase-12 is activated, leading to apoptosis (87).

Autophagy and apoptosis exhibit a complex and dynamic interplay in BC, jointly determining cell fate. Autophagy is a survival mechanism that can suppress apoptosis by clearing damaged organelles, such as dysfunctional mitochondria, and decreasing ROS accumulation, promoting cancer cell survival under chemotherapy stress and leading to therapeutic resistance (92,93). On the other hand, excessive or sustained autophagic activity can result in type II PCD, also known as autophagic cell death, characterized by massive autophagosome formation and degradation of cellular components. Key proteins, such as glucose-regulated protein 78 (GRP78), serve an important role during ER stress. GRP78 activates protective autophagy by inhibiting the mTOR pathway while suppressing apoptosis, thus supporting cell survival under estrogen deprivation or tamoxifen treatment and contributing to endocrine therapy resistance (94,95).

Autophagy serves as a key adaptive mechanism for BC cell survival in the nutrient-deficient TME, such as that of hypoxia or glucose deprivation (96,97). Autophagy is activated under stress conditions to degrade redundant or damaged intracellular

proteins and organelles, recycling key metabolites, such as amino and fatty acids, for energy production and biosynthesis, maintaining cellular energy homeostasis (98). Moreover, the hypoxia signaling pathway mediated by hypoxia-inducible factor-1α (HIF-1α) upregulates autophagy (99), facilitating the clearance of toxic substances generated under hypoxic conditions and sustaining the stemness and self-renewal capacity of BC stem cell populations (100,101). This enables residual cancer cells to enter a dormant state and contribute to disease recurrence (102).

Disruptions in lipid metabolism promote autophagy. Lipophagy is a key autophagy function, in which lipid droplets are selectively degraded to release free fatty acids for β-oxidation and energy production, which is key under glucose-deprived conditions. BC cells typically undergo metabolic reprogramming, while autophagy influences intracellular metabolite levels by regulating amino acid transporters, such as solute carrier family 6 member 14 (SLC6A14). Decreased activity of these transporters disrupts amino acid availability and stimulates autophagy, contributing to endocrine therapy resistance (95). Thus, metabolic dysregulation may modulate autophagic activity by affecting key energy-sensing pathways, such as mTOR and AMP-activated protein kinase (AMPK), forming a metabolic adaptive feedback loop that influences cancer cell survival, proliferation and therapeutic response (103,104).

Pyroptosis. Cell pyroptosis is a type of RCD with lytic and inflammatory characteristics. It is mediated by the cleavage of GSDM family proteins. GSDMD is cleaved by inflammatory caspases (caspase-1, -4, -5, and -11) at a specific site to release its N-terminal domain, which forms pores in the plasma membrane, whereas GSDME is cleaved by caspase-3 at a distinct site, linking apoptosis and pyroptosis (105). This results in cell swelling, lysis and release of pro-inflammatory factors, including IL-1β, IL-18, ATP and HMGB1. Acute pyroptosis activation may induce immune cell infiltration, potentially inhibiting tumor growth (106). GSDM proteins are activated by distinct signaling pathways to execute pyroptotic functions in specific contexts. GSDMD serves as the primary executor of classical inflammatory pyroptosis. It is primarily cleaved by caspase-1 or -4/5/11 activated by inflammasomes, commonly observed during immune cell defense against pathogenic infection (46,107). However, GSDME is typically cleaved by apoptosis-associated caspase-3. When caspase-3 is activated, the cell fate shifts from non-inflammatory apoptosis to inflammatory pyroptosis (108). In addition, granzyme B secreted by CTLs directly cleaves GSDME (109). Overall, inducing cellular pyroptosis within tumors may represent a potential strategy for treating numerous types of cancers. Tumor cells undergoing pyroptosis recruit tumor-suppressing immune cells. Wang *et al* (110) employed a bioorthogonal system to demonstrate that pyroptosis in <15% of tumor cells eliminates entire tumor grafts in live mice. This orthogonal system is capable of controlled drug release by combining nanoparticle-mediated delivery with Phe-boron trifluoride-catalyzed desilylation to selectively release client proteins, including active GSDM, into tumor cells in mice. Zhang *et al* (109) demonstrated that $CD8^+$ T and NK cells induce pyroptosis in tumor cells through granzyme B in a pyroptosis-activated immune ME, establishing a positive feedback loop. However, tumor suppression is abolished in perforin-deficient mice and mice lacking killer lymphocytes. A total of 20/22 tested cancer-associated GSDME mutations decrease its function, indicating that GSDME inactivation may be employed by cancer cells to evade immune attacks. This is particularly relevant in BC. On one hand, genetic mutations directly impair the pore-forming ability of GSDME and decrease the occurrence of pyroptosis. On the other hand, promoter hypermethylation of GSDME is frequently reported in BC, and demethylating treatment can restore its expression and enhance chemotherapy- or immune-induced pyroptosis (108,111). The loss or dysfunction of GSDME in BC allows tumor cells to evade immune surveillance by decreasing pyroptosis and DAMP release, which decreases the infiltration and activation of $CD8^+$ T and NK cells. This loss can result from gene mutations or promoter methylation, suggesting that restoring GSDME expression or function may be a potential strategy to enhance antitumor immune responses.

Phagocytosis. Phagocytosis removes cell debris generated during RCD and breaks it into macronutrients for use by other cells (112). This maintains intracellular environment stability and recycles cell components, providing the necessary material for normal cell function. Specialized cells such as macrophages, neutrophils, monocytes, DCs and osteoclasts are capable of phagocytosis. Phagocytosis is not an isolated cell reaction. It typically occurs concurrently with other cellular processes, such as ROS production, proinflammatory mediator secretion, antimicrobial molecule degranulation and cytokine production (113). Phagocytosis eliminates pathogens and host cells undergoing apoptosis during infection (114).

Phagocytosis is key for antitumor immunity. Specific macrophages enhance the antitumor response through distinct phenotypes and functions. For example, TAMs hinder the efficacy of glioblastoma immunotherapy (115). CD169 macrophages enhance tumor-specific T cell responses by promoting apoptotic glioma cell phagocytosis (116). Inflammatory macrophages regulate macrophage phagocytosis and enhance tumor cell phagocytosis via non-traditional pro-phagocytic integrins such as the CD47/signal regulatory protein α) signaling pathway (117). Additionally, CTL-associated protein 4 (CTLA-4) blockade stimulates microglial cells and enhances tumor cell phagocytosis, promoting antitumor effects (118). Immunotherapeutic strategies may offer novel approaches for glioblastoma treatment by activating synergistic interactions between macrophages and Th1 and microglial cells and by boosting immune cell activation and infiltration.

Tumor cells employ diverse mechanisms within the TME to escape or inhibit phagocytosis, promoting tumor progression and immune evasion. Tumor cells hinder phagocytosis and evade immune clearance by expressing innate immune checkpoints, such as the CD47/SIRPα signaling pathway. Blocking phagocytosis checkpoints enhances phagocytic activity against tumor cells and encourages their clearance (119). PD-L1 expression may hinder T cell cytotoxicity and macrophage-mediated phagocytosis. Disrupting this pathway may trigger antitumor

immunity (120). Overall, phagocytosis serves a pivotal role in pathogen clearance, cellular waste disposal and antitumor defense mechanisms.

4. Nutritional changes due to inflammation and infection

Optimal nutritional status is key for regulating inflammatory and oxidative stress processes, which are connected with the immune system (121). Inflammation is recognized as a primary driver of malnutrition in disease (122). It triggers various physiological responses, such as loss of appetite, decreased food intake, muscle breakdown, and insulin resistance, leading to a catabolic state (122). Patients with colorectal cancer are prone to chronic inflammation, malnutrition and complications arising from chronic nutritional and energy depletion, insufficient dietary intake, stress and metabolic disruptions due to surgeries, chemotherapy or radiation therapy (123). Though most commonly attributed to systemic inflammatory responses, hypoalbuminemia can result from various other causes. For example, liver cirrhosis causes hepatocyte damage and reduced synthetic capacity, while kidney disease leads to increased albumin excretion in urine. Additionally, dietary deficiencies in key amino acids cause decreased albumin levels (124). Albumin serves a key role in maintaining oncotic pressure, neutralizing reactive species and preserving microvascular integrity, thus protecting against inflammatory tissue damage (125). Albumin is the most abundant plasma protein and reflects both nutritional status and inflammatory responses of the host. Recent evidence has demonstrated its independent prognostic value in BC (126). In a large cohort study of nearly 3,000 patients with BC, a low albumin-to-globulin ratio and decreased prealbumin levels were significantly associated with inferior overall survival (OS) and disease-free survival. Importantly, these markers retained independent prognostic significance in multivariate models following adjustment for conventional factors, such as TNM stage and molecular subtype (127). Similarly, serum albumin levels <43 g/l are predictive of shorter OS in an independent cohort of patients with metastatic BC, with low albumin identified as an independent adverse prognostic factor [hazard ratio (HR)=0.47, P<0.01] (128).

Low levels of long-chain n-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid in Western diets may contribute to chronic inflammation (129), as these fatty acids exert anti-inflammatory effects by inhibiting pro-inflammatory cytokine production and modulating eicosanoid synthesis (130). Various dietary and nutrient components, such as omega-3 fatty acids, vitamin A and C and phytochemicals such as polyphenols and carotenoids found in plant foods, possess anti-inflammatory and antioxidant properties. Moreover, dietary fiber in plant foods that is fermented by gut microbiota to produce short-chain fatty acids is associated with health benefits, including anti-inflammatory properties (131).

5. Generation and effects of lipid intermediates

Lipids, including fatty acids, cholesterol and phospholipids, form a diverse group of metabolites crucial for constructing cell and organelle membranes, generating cell energy and engaging in intracellular and hormonal signaling (132). In a healthy organism, free fatty acids undergo β-oxidation to produce ATP and maintain nutrient flux balance. Excess fatty acids are packaged into inert triglycerides using a glycerol backbone and stored in intracellular lipid droplets (133). Excessive nutrition can lead to the accumulation of lipid intermediates in new non-adipose tissue, resulting in lipotoxicity and further tissue damage (134).

Large lipid loads in organ systems impair the efficient fat catabolism and conversion of fatty acids to triglycerides in cells, leading to increased lipogenesis or triglyceride storage in adipose tissue. Glucose oxidation is enhanced in muscle cells, while lipolysis in adipose tissue and fatty acid oxidation in muscle cells increase to provide energy during fasting conditions. These metabolic changes primarily occur in the brain, heart, liver, pancreas, kidney and adipose tissue (135).

In human clinical studies, lipid accumulation is associated with renal dysfunction, while dyslipidemia directly or indirectly impacts the kidney via systemic inflammation, oxidative stress, vascular injury and alterations in signaling molecules such as hormones (136,137). Glomeruli and tubules, especially proximal tubules, are prone to lipid accumulation, contributing to renal injury and dysfunction, which are key factors in diabetic nephropathy (138). Non-alcoholic fatty liver disease is associated with dysregulated lipid synthesis and lipolysis pathways, with studies suggesting decreased lysosomal acid lipase activity in such patients (139,140).

Moreover, endogenous lipid palmitic acid hydroxy stearic acids positively impact blood glucose levels and insulin sensitivity by regulating fat deposition and adipose tissue lipolysis. Long-chain fatty acid oxidation influences postnatal skeletal development. EPA is a long-chain polyunsaturated n-3 fatty acid that regulates fatty acid re-esterification, impacting substrate cycling in human skeletal muscle cells (141). The heart demonstrates the highest energy demand and the most extensive fatty acid oxidation in the body that efficiently accesses circulating lipids. However, increased lipid availability exacerbates ischemia-induced cardiac dysfunction (142). Lipid droplet accumulation in glial cells is hypothesized to offer a protective mechanism against the detrimental effects of neuronal activity by detoxifying toxic fatty acids (143).

Abnormal lipid metabolism and inflammatory responses form a cycle in certain pathological conditions, such as obesity, type 2 diabetes, atherosclerosis and non-alcoholic fatty liver disease, exacerbating disease progression. Lipid accumulation triggers oxidative stress and inflammatory responses, releasing oxidized lipid intermediates that stimulate cytokine production by inflammatory cells, leading to abnormal lipid metabolism (134). The lipid intermediates invade healthy non-adipose tissue, causing lipotoxicity and additional damage. Damaged cells undergo PCD to release more nutrients. During this process, the levels of the primary products of the inflammatory response (lipid intermediates) are amplified, initiating a cycle of deleterious stimuli to the tissues/cells. Free fatty acids can act as endogenous danger signals by binding the TLR4/myeloid differentiation factor 2 (MD2) complex, activating the downstream MyD88/interleukin-1 receptor-associated kinase (IRAK)/TNF receptor-associated factor 6 (TRAF6) signaling pathway. This leads to the activation of the IκB kinase complex and IκB degradation, releasing

NF-κB dimers that translocate into the nucleus to induce the transcription and secretion of pro-inflammatory cytokines, such as IL-6 and TNF-α. This mechanism serves a key role in chronic low-grade inflammation associated with obesity and insulin resistance and contributes to the initiation and progression of cancer such as BC (144,145).

The cycle between abnormal lipid metabolism and inflammation impairs normal cellular and tissue metabolic functions and accelerates the progression of conditions such as atherosclerosis (146), obesity and fatty liver disease (147). In the context of BC, this lipid-inflammation feedback loop contributes to a tumor-promoting microenvironment by enhancing cytokine production, sustaining NF-κB activation and supporting cancer cell survival. It triggers a cytokine storm with the release of large amounts of cytokines, and the dysregulated inflammatory response forms a self-reinforcing feedback loop that may endanger the host (148). The levels of pro-inflammatory cytokines (IL-1, IL-6, TNF and IFN-γ), especially TNF and IFN-γ, are elevated during cytokine storms (149). These factors induce cell death in numerous types of cell, leading to diseases, such as neurological disorder, liver injury, chronic obstructive pulmonary disease, fibrosis and osteoporosis (150). TNF and IFN-γ activation also induces cell death pathways, including pyroptosis, apoptosis and necrosis, further stimulating cytokine release and triggering a cytokine storm (151).

6. Perspectives in BC research

RCD in BC. The link between BC and viral infection is debated in terms of its causes and may interact with other environmental factors to promote tumorigenesis (152,153). DNA from viruses, including human papillomavirus (HPV), Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), herpes simplex virus and Kaposi's sarcoma-associated herpesvirus/human γ herpesvirus 8, have been detected in BC samples (152). However, these viral DNA particles are not present in all BC subtypes and do not control apoptosis, autophagy and pyroptosis in the same way across all subtypes (152). The impact of viral infections can vary depending on the specific BC subtype and the viral mechanisms involved.

High-risk HPV subtypes, particularly HPV16 and HPV18, are most commonly associated with carcinogenic effects and employ unique mechanisms to suppress apoptosis (154). HPV inhibits cancer cell apoptosis by upregulating the tumor necrosis factor receptor superfamily death receptor (155). Furthermore, autophagy inhibition, which is typically mediated by the E7 oncoprotein, exhibits subtype specificity. A study in oropharyngeal squamous cell carcinoma indicated that HPV16 uses E7-mediated degradation of the autophagy and beclin 1 regulator 1 protein to suppress autophagy, rendering cells more sensitive to cisplatin-induced apoptosis (156). By contrast, EBV encodes an anti-apoptotic product that enhances infected cell viability and resistance to chemotherapy, promoting the development of EBV-associated disease (157). HCMV is a slow-replicating virus that has evolved and acquired anti-apoptotic genes, including pUL38 and UL138, which encode apoptosis inhibitors, ensuring HCMV replication by inhibiting apoptosis (158).

Mounting evidence suggests the BC microenvironment is diverse and dynamic, with cell pyroptosis playing a crucial role in its control (159,160). GSDMD and GSDME are key pyroptosis substrates that play key roles in BC etiology and pathogenesis (161). GSDM protein family plays a pivotal role in cellular pyroptosis (162). MicroRNA-200b activates GSDMD by targeting the NF-κB, maternally expressed gene 3 (MEG3), juxtaposed with another zinc finger 1 and JAK2/STAT3 pathways, whereas uncoupling protein 1, dopamine receptor D2, the AMPK/SIRT1/NF-κB/BAK and the STAT3/ROS/JNK pathway activate GSDME (163). Additionally, some PRRs, such as absent in melanoma 2, melanoma differentiation-associated gene 5 and RIG-I, can activate GSDME (164). Furthermore, complexes containing PD-L1 and STAT3 upregulate GSDMC expression under hypoxic conditions (165).

Multiple mechanisms prevent apoptosis in BC TME. Cancer-associated fibroblasts (CAFs) secrete factors such as IL-6 and CXCL12 that activate survival pathways in cancer cells, enhancing their resistance to apoptosis (166). TAMs produce cytokines, such as IL-10 and TGF-β, which promote tumor cell survival (70). Additionally, the hypoxic conditions within tumors induce HIF-1α expression, leading to the upregulation of anti-apoptotic proteins such as Bcl-2 and survivin (167). These factors create an environment that supports cancer cell survival and proliferation by inhibiting apoptotic pathways (168).

The inflammatory microenvironment in BC continuously shapes RCD pathways through persistent signaling, consequently influencing tumor progression (169). Pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α, activate key signaling cascades, such as NF-κB, JAK/STAT3, and PI3K/AKT. These drive the transcription of anti-apoptotic molecules such as Bcl-2, Bcl-xL and X-linked inhibitor of apoptosis protein, while simultaneously suppressing Bax/Bak-mediated mitochondrial outer membrane permeabilization and blocking cytochrome c release (170). This weakens the mitochondrial apoptotic response and allows tumor cells to maintain survival advantages under adverse conditions. At the same time, these signals alter inflammatory cell death modalities, for example, by activating the NLRP3/caspase-1/GSDMD or GSDME pathways to promote pyroptosis, inducing immune activation and T cell infiltration (171). Pyroptosis may be attenuated in the absence of effector molecules or when signals are reprogrammed, enabling tumors to evade immune surveillance (172). The inflammatory microenvironment in BC exhibits both pro-tumor and antitumor potential through this dynamic regulation of both the threshold and mode of cell death, ultimately determining the course of disease progression and therapeutic responses.

Immune system in BC. The innate immune system is key for BC immunity. It comprises innate lymphocytes (ILCs), whose differentiation and function are associated with the immune response (173,174). ILCs are a newly discovered class of innate immune cell derived from pluripotent hematopoietic stem cells (175). These cells are predominantly found in tissue and are common on the mucosal surfaces of the lung and intestines (176). ILCs are divided into three groups. The first group includes ILC1s and NK cells, the second group comprises ILC2s and regulatory ILCs (ILCregs) and the third group consists of ILC3s and lymphoid tissue-inducing cells (177). ILC1s are characterized by their ability to produce

IFN-γ and are key in the early BC stages due to their role in activating cytotoxic immune responses. In advanced tumors, ILC1s are typically induced by factors such as TGF-β in the TME to drive the conversion of NK cells into an ILC1-like phenotype (178-180). These cells lose their potent cytotoxic activity and promote angiogenesis and immune tolerance via secretion of factors such as VEGF. At the same time, ILC1s within tumor tissue commonly upregulate multiple immune checkpoint receptors, including NKG2A, killer cell lectin-like receptor subfamily G member 1, CTLA-4, CD96 and LAG3, leading to marked functional suppression. Overall, they exhibit immunosuppressive and tumor-promoting effects (181). ILC2s produce type 2 cytokines, including IL-4, IL-5 and IL-13, and are involved in tissue repair and immune regulation. However, their role in cancer is either promotive or inhibitory depending on the context. ILC3s produce IL-17 and IL-22, contributing to both pro-inflammatory and tissue-regenerative processes. Their role in tumor development can also vary (182).

Myeloid cells, notably granulocytes, macrophages and DCs, are crucial for maintaining immune system homeostasis and exert key effects within the TME (183). Myeloid-derived suppressor cells (MDSCs) are immune-suppressive cells that serve a key role in BC development and progression. Their regulatory mechanisms involve multiple cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), VEGF and interleukins (IL-1, IL-6, IL-13, IL-17, IL-20, IL-33 and IL-34), as well as signaling pathways, including the STAT family (STAT3, STAT6), NF-κB, Notch, ER stress response and JAK/STAT and PI3K/AKT/mTOR cascades (184). The complement system activity is crucial in BC immunity, with components such as C1q, C3a, and C5a associated with tumor growth, metastasis and immune responses (185). The complement system also promotes tumor progression through various mechanisms by enhancing angiogenesis, suppressing antitumor immune responses and aiding in the creation of a tumor-friendly microenvironment (186). Additionally, host defense peptides and antimicrobial agents have antitumor activity against cancer cells (187).

B and T cells from the adaptive immune system are key for the antitumor response. B cells secrete antibodies and regulate immune responses. Activated B cells infiltrating tumors have antitumor effects in BC (188). Regulatory B cells may influence the tumor immune microenvironment by secreting inhibitory factors such as IL-10 and TGF-β (189). T cells, notably $CD4^+$ and $CD8^+$ T cells, are key in BC. $CD8^+$ T cells directly eliminate cancer cells via CTL production, while the differentiation status and secreted cytokines of $CD4^+$ T cells impact the immune response direction (190). Th1 cell activity contributes to tumor growth inhibition and spread (191). Moreover, T regulatory cells (Tregs), a subset of $CD4^+$ T cells characterized by transcription factor FOXP3 expression, play a critical role in maintaining immune homeostasis and preventing autoimmune responses. Tregs also contribute to immunosuppression in cancer by inhibiting the function of effector T cells, including $CD8^+$ CTLs, which can facilitate tumor progression (192). Additionally, T cell exhaustion, which is marked by the upregulation of inhibitory receptors, such as PD-1 and CTLA-4, leads to a dysfunctional state in which T cells lose their effector functions, contributing to the immunosuppressive TME (193). Additionally, specific immunomodulatory proteins such as prolactin-inducible protein are crucial in BC immunomodulation, and their absence may result in tumor development (194).

BC cells typically downregulate MHC-I molecules via epigenetic mechanisms to evade immune surveillance, with DNA methylation and histone modification serving key roles. DNA methyltransferase-mediated promoter hypermethylation can silence genes, such as human leukocyte antigen (HLA)-A/B/C and β2-microglobulin, while also suppressing the expression of antigen-processing components, including transporter associated with antigen processing (TAP)1/2, thereby weakening antigen presentation. At the same time, the EZH2/PRC2 complex suppresses transcriptional regulators such as CIITA via H3K27me3 modifications, further reducing MHC-I transcription. As a result, the surface expression of MHC-I on BC cells is markedly diminished, leading to impaired recognition by $CD8^+$ T cells, resulting in immune evasion (195,196).

Platelets are known for their role in hemostasis and thrombosis (197). They are increasingly recognized for their impact in the BC microenvironment (198,199). Platelets promote BC growth and metastasis through various mechanisms (200). They form aggregates with tumor cells, protecting them from shear stress in the bloodstream and immune system attacks, such as those by NK cells. Platelet-released factors such as platelet factor 4 contribute to tumor angiogenesis and metastasis (201). Chemokines released by platelets, such as CXCL12 and CXCL4, enhance the migratory and invasive ability of tumor cells, further driving metastasis (202). Platelets also promote epithelial-mesenchymal transition in tumor cells by releasing chemokines and cytokines, endowing tumor cells with greater migratory and invasive capability (203).

Glycolytic reprogramming (the Warburg effect) in the TME provides energy and metabolic intermediates for tumor cells and impairs the antitumor functions of the immune system via multiple mechanisms (204). Excessive lactate accumulation leads to local acidification, which directly suppresses the effector activity of cytotoxic T and NK cells, while decreasing the production of key cytokines, such as IFN-γ and TNF-α (205). At the same time, the high glucose demand of tumors creates energy competition, placing T cells and DCs in a metabolically restricted state, thus diminishing their proliferative capacity and antitumor responses (206). Lactate also drives TAMs toward an immunosuppressive M2 polarization and hinders DC maturation, further promoting MDSC accumulation and shaping an immunosuppressive microenvironment (207). In addition, glycolytic metabolites activate signaling pathways, such as HIF-1α, and induce PD-L1 upregulation, inhibiting T cell function through immune checkpoint mechanisms (196,208,209).

In summary, the interplay between the innate and adaptive immune systems, coupled with the regulatory roles of diverse cells and molecules, is key in the onset, progression and treatment of BC. Gaining a deeper understanding of these mechanisms may aid in devising more effective immunotherapy strategies, enhancing the survival and quality of life for patients with BC.

Inflammatory response in BC. BC development is associated with inflammation, which is marked by the presence of immune

system and other inflammation-associated cells in its tissues. Infiltration of inflammatory cells, including lymphocytes, macrophages, DCs, monocytes and neutrophils, is a common characteristic of BC (210). It can result in the release of inflammatory factors, such as IL-17A and IL-6, which activate pathways associated with cancer and facilitate BC development (211). Studies have demonstrated an association between the degree of inflammatory cell infiltration in BC tissue and cancer survival (212,213). Specifically, the presence of $CD8^+$ T cells within the tumor is linked to patient survival (214). Notably, IL-6 serves an important role in the inflammatory microenvironment of BC, particularly in aggressive subtypes, including TNBC and $HER2^+$ BC. IL-6 promotes tumor progression and metastasis via the JAK/STAT3 signaling pathway in TNBC, and high IL-6 serum levels are associated with poor prognosis (215,216). IL-6 contributes to trastuzumab resistance in $HER2^+$ BC by expanding cancer stem cell populations via an autocrine inflammatory loop (217). These findings highlight the potential of targeting IL-6 signaling as a therapeutic strategy in specific BC subtypes.

Inflammatory cytokines in BC regulate the balance between apoptosis and autophagy through multiple signaling pathways, influencing cell fate. Studies have shown that TNF-α and IL-1β can upregulate the expression of the anti-apoptotic Bcl-2 via the NF-κB pathway, inhibiting mitochondrial-mediated apoptosis (218,219). However, TNF-α also activates the JNK pathway under strong inflammatory stimulation to promote Bax/Bak-mediated mitochondrial membrane permeabilization, ultimately inducing caspase cascades and triggering apoptosis (220). At the same time, IFN-γ enhances the expression of effector molecules, such as caspase-3, through the JAK/STAT1 pathway, amplifying apoptotic effects. Furthermore, IL-6 suppresses autophagic activity via the JAK/STAT3/mTOR signaling pathway, helping BC cells to maintain survival and acquire drug resistance under adverse conditions (221). The IL-6/STAT3 pathway, persistently activated in TNBC and some $HER2^+$ BC, not only suppresses autophagy but also induces PD-L1 expression, driving immune evasion and serving as a key target for combined immunotherapy (222). The NLRP3 inflammasome and its downstream caspase-1/GSDMD pyroptotic pathway can both promote metastasis via IL-1β secretion and trigger immunogenic cell death, thus offering bidirectional therapeutic value. Hypermethylation-mediated silencing of GSDME dampens pyroptosis-associated immunogenic signals, whereas demethylating agents restore GSDME expression and enhance the efficacy of immunotherapy (223). In addition, the IL-17A/STAT3/VEGF axis promotes angiogenesis and immunosuppression, making it a promising target to block metastasis (11). Thus, inflammatory cytokines are not only inducers of cell death but also remodel the dynamic balance between autophagy and apoptosis through key pathways, such as NF-κB, JAK/STAT and mTOR, impacting BC progression and therapeutic responses.

The association between inflammatory factors and BC risk has been reported in multiple studies (224,225). The strength of the role served by different inflammatory factors in BC pathogenesis varies. IL-17 confers the hazard risk (HR=2.65), with IL-1β [odds ratio (OR)=1.71] and IL-6 [relative risk (RR)=1.58] also associated with increased risk (226,227). The risks associated with TNF-α (RR=1.36) and IL-8 (OR=1.09) are slightly increased, while IL-1α (OR=1.01) is not associated with increased risk (Fig. 2) (226-228).

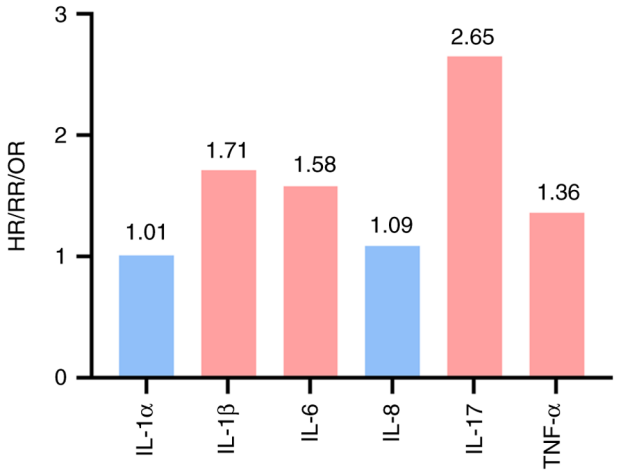

Figure 2. Association between inflammatory cytokines and breast cancer risk (226-228). Red indicates inflammatory factors that significantly increase breast cancer risk, while blue indicates those with no significant effect. HR, hazard ratio), RR (relative risk), OR (odds ratio).

Numerous types of inflammatory cell play distinct roles in BC. For example, macrophages serve key roles in chronic inflammation associated with BC and can adopt M1 or M2 phenotype (229). M1 macrophages release pro-inflammatory cytokines, including TNF-α, IL-1 and IL-6, as well as reactive oxygen and nitrogen species, which influence tumor proliferation, invasion and metastasis. By contrast, M2 macrophages release anti-inflammatory cytokines, such as IL-10, CCL5 and TGF-β, which contribute to tissue repair and tumor progression. IL-6 exerts both pro- and anti-inflammatory effects (230). However, the concept that pro-inflammatory M1 and anti-inflammatory M2 macrophages play opposing roles in inflammation is oversimplified due to the high plasticity of these cells in response to microenvironmental stimuli (231). Moreover, the abundance of macrophages is associated with clinical characteristics and prognosis of BC (232).

Conversely, the presence of cancer-associated adipocytes and corpuscular structures within BC tissue also significantly influences tumor development (233). Cancer-associated adipocytes secrete diverse inflammatory factors that alter BC cell behavior, thereby promoting tumor invasion and metastasis (233). On the other hand, corpuscular structures comprise macrophages, which serve as histological indicators of pro-inflammatory processes and are present in adipose tissue adjacent to BC (234). These cells release pro-inflammatory factors that may induce a chronic inflammatory state, influencing tumor progression and prognosis.

Mesenchymal stem cells (MSCs) and CAFs serve key roles in inflammatory processes associated with BC. MSCs secrete chemokines and cytokines that influence tumor growth and metastasis. MSCs have been shown to promote tumorigenesis by differentiating into CAFs and enhancing the immunosuppressive environment, leading to increased tumor cell proliferation and invasion (235). CAFs represent one of the predominant stromal cell populations in BC and

participate in inflammation-mediated TME regulation. CAFs contribute to tumorigenesis by remodeling the extracellular matrix, promoting angiogenesis and secreting factors, such as TGF-β, VEGF and IL-6, which enhance the metastatic potential of tumor cells (236). CAFs are involved in resistance to chemotherapy and targeted therapies by creating a protective niche for cancer cells and modulating immune cell infiltration (237). This dual role of MSCs and CAFs underscores their importance in BC progression and treatment resistance.

Chronic inflammation is associated with BC development and may also accelerate metastatic progression. Immune cells and inflammatory mediators in the inflammatory microenvironment enhance tumor cell migration and invasion, thus elevating metastatic risk. Similarly, inflammation exerts beneficial antitumor effects in the early stages of tumor development. IFN-γ is a key factor in this process, as it upregulates MHC-I expression in tumor cells, enhances antigen presentation and promotes DC-mediated $CD8^+$ T cell activation, enabling them to directly kill tumor cells (238,239). Inflammation strengthens the functions of NK cells and macrophages, further eliminating abnormal cells and providing long-term surveillance via the formation of immune memory, protecting the host during the initial tumorigenesis stages (240). Thus, deeper comprehension of chronic inflammation in BC is key for devising more efficacious therapeutic approaches, potentially improving patient prognosis and guiding future research.

Overnutrition and BC. Overnutrition is a notable risk factor for various human diseases, especially those associated with obesity, such as neurodegenerative diseases, metabolic disorder and cancer (241). Therefore, adopting a reasonable fasting regimen is key. Fasting has notable lasting positive effects on multiple health indicators by improving insulin sensitivity, lowering blood pressure, decreasing body fat content and stabilizing blood glucose levels and lipid metabolism (242). The relationship between obesity and BC has garnered notable attention (243,244). The biological effects of obesity extend beyond weight gain to include inflammatory responses, endocrine alterations and metabolic dysregulation, which are factors that collectively promote BC initiation and progression (245,246).

Obesity increases systemic inflammatory responses and drives metabolic disorder, including insulin resistance, hyperinsulinemia and dysregulated lipid metabolism. These metabolic abnormalities impair immune surveillance through multiple mechanisms. For example, hyperinsulinemia and elevated insulin-like growth factor 1 (IGF-1) signaling enhances tumor cell proliferation and survival by activating the PI3K/AKT/mTOR pathway (247,248). Obesity-associated lipid accumulation skews macrophages toward an M2-like immunosuppressive phenotype and impairs DC maturation, weakening antigen presentation (249). In addition, chronic low-grade inflammation leads to persistent IL-6, TNF-α and leptin secretion, which promotes Treg expansion and MDSC recruitment and decreases $CD8^+$ T cell cytotoxicity (250,251). Collectively, these metabolic-immune alterations create a permissive TME that facilitates BC cell proliferation, immune evasion and therapeutic resistance.

The association between obesity and BC is a complex and multifactorial research area that has attracted attention (252,253). Epidemiological evidence indicates that each 1 kg/m^2 increase in body mass index (BMI) is associated with a ~3.4% increase in BC risk in postmenopausal patients [RR=1.034; 95% confidence interval (CI): 1.020-1.048]. Higher BMI shows a neutral or inverse association with BC risk in premenopausal patients (RR=0.79; 95% CI: 0.70-0.88) (254). Severe obesity (BMI ≥35 kg/m^2) further increases the risk, with HR of ~1.58 (95% CI: 1.40-1.79) for invasive BC and ~1.86 (95% CI: 1.60-2.17) for the ER^+/PR^+ subtype (255). Overweight and obese patients are at a higher risk for lymph node-positive disease (HR=1.64; 95% CI: 1.09-2.48) and ER^+ tumors (HR: 1.20-1.40) (256). Weight gain after adulthood is also a key factor, with each 5 kg increase in body weight associated with ~12% higher risk of postmenopausal BC (257).

Adipokines are bioactive hormones originating from adipose tissue that regulate metabolism, caloric intake, angiogenesis and cell proliferation. Adipokine levels typically become dysregulated in obesity and are associated with cancer development and metastasis (258). Lipid metabolism influences BC proliferation, migration and apoptosis (259). Lipids are key to cellular structure and play pivotal roles in intercellular signaling and metabolism (260). Research indicates that cancer cells require substantial lipid amounts for synthesizing biofilms, organelles and signaling molecules that drive tumor progression (261). Chronic inflammation of white adipose tissue is a crucial mechanistic link between obesity and elevated BC risk (262). Activated macrophages and elevated inflammatory mediators (IL-6, TNF-α and IL-1β) amplify both local and systemic inflammation in obesity, reshaping the TME and promoting angiogenesis, proliferation and metastasis (263).

Cholesterol is a notable lipid component that plays a vital role in BC pathogenesis. High cholesterol levels are associated with increased BC risk and progression (264). Studies have shown that BC cells exhibit altered cholesterol metabolism, which promotes tumor growth and metastasis (265,266). Cholesterol influences BC cell signaling pathways, such as the PI3K/AKT and ERK pathways, contributing to cancer cell survival and proliferation. Moreover, cholesterol-rich lipid rafts in the cell membrane serve as platforms for oncogenic signaling. For instance, cholesterol involvement in the PI3K/AKT pathway leads to the activation of a key regulator of cell proliferation and survival, mTOR, thereby promoting tumor development (267). The ERK pathway is modulated by cholesterol and serves a crucial role in cell division and differentiation, further aiding cancer progression (268).

Cholesterol also affects the composition and fluidity of cell membranes, influencing the function of membrane-bound proteins involved in signal transduction (269). This modulation enhances the ability of cancer cells to invade surrounding tissue and metastasize. Furthermore, the interaction between cholesterol and caveolin-1, a structural protein in caveolae (specialized lipid rafts), is implicated in tumorigenesis regulation (270).

Elevated circulating estrogen levels are associated with a higher risk of hormone-sensitive BC (271). Peripheral adipose tissue becomes the primary site of estrogen

production during the postmenopausal period, where aromatase converts androgens into estrogens. Excessive adipose tissue leads to higher circulating estrogen levels with an increasing BMI, contributing to an increase in BC incidence (272). However, this appears to contradict the decrease in circulating estrogen levels following menopause, which may demonstrate the complex association between obesity and BC (273).

Metabolic syndrome and insulin resistance are associated with BC development and prognosis. Hyperinsulinemia is associated with heightened synthesis of IGF-1, activating signaling pathways that enhance cancer cell proliferation, migration and survival (274). Insulin also serves a key role in lipid metabolism (275). Elevated insulin levels, characteristic of insulin resistance, trigger lipolysis and the release of substantial amounts of free fatty acids, impacting metabolic health status and establishing a detrimental cycle (276,277).

In summary, the association between obesity and BC involves a complex, multifactorial process that involves the interaction of various biological mechanisms. A thorough understanding of these mechanisms may aid in more effective prevention and treatment of BC, especially in obese patients.

7. Future of the immune system in BC treatment

Traditional treatments for BC, such as surgical excision, radiotherapy, chemotherapy and endocrine therapy, are not universally applicable and have a range of side effects. Thus, identifying novel treatment strategies is key for enhancing the prognosis of patients with BC. Immunotherapy, which comprises both passive and active approaches, has potential in treating various cancers (278,279). Passive immunotherapy involves the administration of immune components, such as monoclonal antibodies (trastuzumab), to directly target tumor cells. Active immunotherapy aims to stimulate the host immune system to attack tumors. These strategies include ICIs, cancer vaccines and cellular therapy (280).

Subtype-specific immunotherapeutic strategies are key given the heterogeneity of BC. For example, combining trastuzumab with IL-6R inhibitors (tocilizumab) in $HER2^+$ BC has shown promise in overcoming resistance mediated by IL-6-driven cancer stem cell expansion (217). Dual blockade of IL-6 and CCL5 signaling has been demonstrated to synergistically inhibit tumor growth and metastasis in TNBC (216). Ongoing clinical trials are evaluating the efficacy of IL-6 pathway inhibitors in combination with standard therapies for patients with metastatic $HER2^+$ BC and TNBC, underscoring the translational potential of targeting inflammatory pathways in BC immunotherapy (281-283).

Immunotherapeutic approaches for BC involve therapies using humanized monoclonal antibodies that target altered molecules expressed by cancer cells (284). Trastuzumab is a humanized monoclonal antibody approved in 1998 for $HER2^+$ BC that represents a key therapeutic advancement (285). Trastuzumab is traditionally classified as a molecularly targeted drug because it inhibits HER2-mediated signaling and blocks downstream proliferation pathways (286). However, growing evidence indicates that its therapeutic effects also depend on immune-mediated mechanisms, particularly antibody-dependent cellular cytotoxicity (ADCC) (287,288). In this process, the Fc fragment of trastuzumab binds FcγRIIIa (CD16) on the surface of NK cells, prompting them to release perforin, granzyme and pro-inflammatory cytokines, such as IFN-γ and TNF-α (287). This leads to tumor cell lysis and recruitment of other immune cells to participate in the response. The dual action links HER2 signaling inhibition with immune activation, enabling trastuzumab and other HER2-targeted antibodies to be incorporated into cancer immunotherapy (289). HER2-targeted drugs suppress oncogene signaling and mobilize the immune response, highlighting their dual attributes as both targeted therapy and immunotherapy (288,290). Other anti-HER2 agents, including the monoclonal antibody pertuzumab and small molecule tyrosine kinase inhibitors (lapatinib, neratinib, gefitinib and afatinib), have subsequently been used (291). Monoclonal antibodies primarily exert immune-mediated effects such as ADCC, while tyrosine kinase inhibitors function via intracellular signal blockade (292). Nevertheless, monoclonal antibody therapy encounters challenges, including moderate remission rates and drug resistance development (293). Another strategy involves the use of antibody-drug conjugates and T cell bispecific antibodies (294). The IMpassion130 trial demonstrated that atezolizumab combined with nab-paclitaxel improves progression-free survival in patients with TNBC, but the clinical benefit is confined to the PD-L1-positive subgroup (295). The aforementioned trial did not show a significant OS advantage in the intention-to-treat population and was discontinued due to the lack of efficacy in the overall cohort (295).

Notable progress has been made in immunotherapy based on BC subtypes. Clinical trial, such as KEYNOTE-355, have confirmed that PD-1 inhibitors (pembrolizumab) combined with chemotherapy significantly improve progression-free survival and OS in TNBC, and this regimen has been approved by the US Food and Drug Administration as a first-line standard treatment (296). Antibody-drug conjugates, such as trastuzumab deruxtecan, have demonstrated efficacy in later-line treatments for $HER2^+$ BC and are being investigated in combination with ICIs (297). In addition, cancer vaccines, bispecific antibodies and cell therapies are also increasingly explored in subtype-stratified BC treatments (298,299). There are notable differences in the immune response rate to PD-L1 inhibitors between patients, which may be associated with biomarkers, such as tumor-infiltrating lymphocyte (TIL) density, PD-L1 expression heterogeneity and tumor mutational burden (TMB) (300). Integrating molecular biomarkers, including PD-L1 expression, TIL density and TMB, with the immune microenvironment status to guide personalized treatment represents a key direction for improving therapeutic efficacy (178,301).

Immune evasion mechanisms in BC involve alterations in both the TME and tumor cells. Tumor immunogenicity depends on BC subtype. For example, HER2-positive BC and TNBC exhibit distinct immunogenic characteristics (297). Tumor cell recognition is key for the success of immunotherapy, and elevated estrogen levels may interfere with immune system activity (302). Therefore, combining

anti-estrogen therapy with immunotherapy may represent a reasonable strategy. Furthermore, the anti-apoptotic tumor cell mechanisms and HLA-I expression also impact the efficacy of immunotherapy (303). Targeting alterations in tumor cells, such as via combination therapy with inhibitors, may enhance clinical benefits for patients and alleviate treatment resistance. Overall, the success of BC immunotherapy depends on overcoming the tumor immune evasion mechanisms, optimizing the TME and enhancing tumor cell recognition, which require consideration of both tumor characteristics and individual patient differences.

The primary mechanism of BC vaccines is to activate antigen-specific T cells, which target and eliminate cancer cells (304). BC vaccines are classified into those targeting HER2 or associated antigens and those targeting non-HER2-associated antigens. The E75 vaccine is a safe and effective immunotherapeutic agent that induces a peptide-based immune response. A clinical trial demonstrated that the E75 vaccine significantly decreases cancer recurrence in 95.2% of patients with high-risk BC expressing HER2 when combined with booster immunization (305). GP2 exhibits lower HLA-A2 affinity compared with E75, but it may have higher immunogenicity levels. GP2 induces T cell responses and delayed-type hypersensitivity when administered concurrently with GM-CSF in patients with high-risk BC (306). The AE37 vaccine is typically used as adjuvant immunotherapy for BC (307).

As an emerging field in BC treatment, immunotherapy faces challenges, such as low complete remission rates and increased adverse events. Successful treatment involves overcoming tumor immune evasion mechanisms and optimizing the TME to enhance tumor cell recognition. Integrating individual patient differences may help develop more effective treatment regimens.

8. Conclusion

The immune system, inflammatory response and RCD are interconnected in BC, collectively influencing tumor progression and treatment outcomes. The immune system is typically suppressed in patients with BC, leading to immune evasion by the tumor. Prolonged chronic inflammation promotes tumor development and is associated with the malignant features of BC. Cytokines and inflammatory mediators produced during inflammation affect the proliferation, invasion and metastatic potential of tumor cells. Abnormal regulation of apoptosis and autophagy in BC cells leads to tumor proliferation and survival. Aberrant regulatory mechanisms of RCD include apoptosis evasion and autophagy inhibition. These abnormalities are associated with drug resistance and malignant tumor characteristics. Studying the mechanisms and regulation of these interactions may deepen understanding of BC development and progression, offering novel strategies for its prevention and treatment. In recent years, immunotherapy has achieved progress in BC treatment, particularly that of TNBC (328). Pembrolizumab combined with neoadjuvant chemotherapy significantly improves pathological complete response rates in high-risk patients with early TNBC and demonstrates favorable efficacy and safety in clinical practice (KEYNOTE-522 and KEYNOTE-756 Phase III trials and real-world studies) (309-311). These data support immunotherapy as a standard treatment approach in high-risk early TNBC and highlight the importance of individualized treatment strategies. Future research directions should focus on BC subtypes and the role of cytokines in the TME, while also adopting advanced technical strategies. Single-cell RNA sequencing is used to map the transcriptional profiles of immune cells across BC subtypes in order to delineate subtype-specific immune regulatory networks. Gene-editing approaches, such as clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9), may be employed to investigate the functional roles of key cytokines in tumor progression and therapeutic resistance to establish causal mechanisms. Moreover, integrating these approaches with spatial transcriptomics or proteomics may further uncover cell-cell interactions and microenvironmental heterogeneity. Together, these strategies may provide more precise insight and promote the development of personalized immunotherapeutic approaches.

Future research should focus on the roles of inflammatory factors and cell death-associated pathways in different molecular subtypes of BC, with particular attention to the key functions of IL-6, IL-1β, TNF-α and their associated signaling pathways in driving immune evasion and therapy resistance (312). It is also important to address the loss of immunogenicity caused by the silencing of GSDME through promoter methylation, which impairs pyroptosis, as well as the decrease in antigen presentation resulting from the downregulation of PD-L1 and HLA-I (313,314). In addition, attention should be given to obesity-associated inflammatory factors and abnormal lipid metabolism, which contribute to an immunosuppressive TME. Approaches such as single-cell RNA sequencing and spatial transcriptomics can be employed to map the distribution and interactions of immune cells and these key factors across BC subtypes (315). Functional validation of molecules such as IL-6, GSDME and TAP1/2 can be performed using CRISPR/Cas9 technology in patient-derived organoids and humanized mouse models. Furthermore, the effects of modulating epigenetic states and metabolic pathways on immune cell infiltration and treatment responses can be explored. Integrating these findings with large-scale clinical data to analyze the associations between these key molecules and patient prognosis and treatment outcomes may provide novel targets and evidence-based support for the development of more precise, subtype-specific immunotherapy combinations for BC, such as ICIs combined with IL-6 inhibitors or epigenetic drugs.

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Authors' contributions

GL, BJ and JZ wrote the manuscript. ZF and SF revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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