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The Role of Alarmins in Breast Cancer

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Abstract: Breast cancer (BC) remains the most common malignant tumor in women globally, with its incidence and mortality ranking first and second among female cancers, respectively. Despite continuous innovation and progress in modern medicine, current clinical treatment strategies for breast cancer still face high mortality rates. Therefore, developing new therapeutic targets and strategies is urgently needed. Alarmins are a class of endogenous molecules released during non-programmed cell death (such as infection or injury), and they typically serve as early warning signals for the immune system. Early research primarily focused on the role of alarmins in autoimmune and immune-mediated diseases, but recent studies have shown that alarmins also play a crucial role in the development, progression, and therapeutic response of breast cancer. In this review, we will discuss the role of alarmin family members (such as HMGB1, S100A8, S100A9, and IL-33) in breast cancer and their potential as therapeutic targets.

Keywords: Alarmins; Hmgb1; S100A8; S100A9; IL-33; Breast Cancer.

1. Introduction

Breast cancer remains the most common malignant tumor in women worldwide, posing a serious public health challenge [1]. Although there have been significant advancements in early diagnosis and treatment technologies for breast cancer, many patients continue to die from disease recurrence or drug resistance [2]. Therefore, it is essential to deeply explore the molecular mechanisms of breast cancer, identify and validate new therapeutic targets, in order to improve treatment efficacy and patient prognosis.

Alarmins are endogenous, constitutively expressed, chemotactic, and immune-activating proteins/peptides that are released in response to degranulation, cell damage, cell death, or immune induction. They possess a potent pro-inflammatory effect, stimulating innate immunity and triggering antigen presentation, which then activates adaptive immune responses [3]. Additionally, alarmins can interact with chemotactic and pattern recognition receptors (PRRs), acting as intercellular signaling defenses that stimulate immune cells in host defense [4]. The alarmin family includes: 1. antimicrobial peptides and proteins (AMPs), such as defensins, antimicrobial peptides, eosinophil-derived neurotoxin (EDN), and granulysin; 2. Nuclear binding proteins (HMGB1 and interleukin [IL]-1α); 3. Heat shock proteins (HSPs), such as HSP60 and HSP96; 4. Ion-binding agents (such as S100A8, S100A9, and lactoferrin); 5. Nucleotides/metabolites (ATP and uric acid); 6. Extracellular matrix degradation products [5].

It has been reported that the expression level of the alarmin protein HMGB1 in breast cancer tissue is significantly higher than in patients with benign breast diseases or normal populations, suggesting that serum HMGB1 could serve as a potential diagnostic biomarker for breast cancer [6]. Additionally, the aberrant expression of HMGB1 has been shown to be closely linked to the proliferation, invasion, and metastasis of breast cancer cells [7, 8]. With the progress of immunological research, the promotive role of IL-33 in breast tumor formation and the transcriptional activation of S100A9 in the progression of triple-negative breast cancer have further elucidated the functional role of alarmins in breast cancer [9, 10]. Therefore, this review will focus on discussing the role of alarmins in breast cancer and their potential clinical applications.

2. HMGB1 in Breast Cancer

High mobility group protein box 1 (HMGB1) is a highly conserved member of the high-mobility group protein superfamily, distributed both intracellularly and extracellularly [6, 11]. HMGB1 is expressed in various tumor tissues, and its different subcellular localizations within tumor cells dictate its diverse regulatory functions in tumor development and progression.

In the nucleus, HMGB1 can directly interact with p53, retinoblastoma protein (RB), and NF-κB family members, enhancing its oncogenic effects [8, 12, 13]. Classical DNA repair pathways have been shown to be regulated by nuclear HMGB1, which participates in the repair of DNA damage caused by chemotherapy or radiotherapy [14-16]. In the cytoplasm, HMGB1 mainly contributes to tumor cell survival and drug resistance through the regulation of autophagy [17]. Extracellular HMGB1 has biological activities that promote cell proliferation, migration, and tissue regeneration [18]. Moreover, HMGB1 can exert chemotactic effects in the extracellular space, enhancing the upregulation of vascular adhesion molecules, which disrupts epithelial barrier function and coordinates immune responses in the tumor microenvironment [19]. During tumor progression, HMGB1 is continuously expressed and facilitates tumor proliferation, invasion, and immune tolerance through specific post-translational modifications [20, 21]. Therefore, the functional roles of HMGB1 in different subcellular locations are of significant importance for tumor regulation.

In clinical research, serum HMGB1 levels were measured by ELISA in normal individuals, breast cancer patients, and those with benign breast diseases. The results indicated that

HMGB1 expression in both breast tissue and serum was significantly higher in breast cancer patients than in those with benign breast conditions or normal controls, suggesting that serum HMGB1 could be a potential biomarker for breast cancer [6]. Additionally, studies have indicated that after neoadjuvant chemotherapy (NACT) in breast cancer patients, the levels of HMGB1 and E-cadherin significantly decreased, and changes in HMGB1 levels were found to be correlated with chemotherapy response [22]. Therefore, it is crucial to conduct in-depth research on the role of HMGB1 in breast cancer.

(1) The Impact of HMGB1 on Breast Cancer Development and Progression

During different stages of tumor growth, HMGB1 is continuously expressed and promotes tumor proliferation, invasion, and immune tolerance through specific post-translational modifications [20, 21]. Currently, several post-translational modification regulators (such as miR-107, miR-129-5p, miR-200c, and miR-205) have been found to regulate the expression of HMGB1[23-27]. These miRNAs are typically involved in cell proliferation, migration, and responses to therapy. Moreover, activation of the HMGB1/RAGE signaling axis has been shown to play a key role in tumor cell proliferation, migration, signal transduction, and chemotaxis [28-30].

HMGB1 directly enhances breast cancer cell proliferation by interacting with retinoblastoma protein (RB). RB protein forms a docking bridge between HMGB1 and E2F1 by binding to the LXCXE motif of HMGB1. Research shows that the interaction between HMGB1 and RB protein is essential for regulating cell proliferation, inducing G1 phase cell cycle arrest, and promoting tumor growth [31]. Further research revealed that the interaction between HMGB1's LXCXE motif and RB protein is a key factor. By constructing a mutant of the HMGB1 LXCXE motif, the study showed that this mutation disrupted the binding of HMGB1 to RB protein, and through the LXCXE-dependent mechanism, HMGB1 significantly inhibited the proliferation of breast cancer cells [8].

The mechanisms of HMGB1 in migration and invasion have been extensively studied in breast cancer research. For instance, Ni et al. found that silencing HMGB1 significantly suppressed the migration and invasion of breast cancer cells [7]. HMGB1 promotes angiogenesis and migration in breast cancer through the PI3K/AKT/HIF-1α pathway [32]. Additionally, the HN1L protein interacts with HSPA9 to upregulate HMGB1 expression, thus playing a crucial role in the invasion and metastasis of breast cancer cells [33]. Chen et al. found that the expression of circRNA CHIPK3 is upregulated in breast cancer, activating the HMGB1/PI3K/AKT signaling pathway, which not only promotes breast cancer cell proliferation but also enhances migration and invasion abilities [34]. Extracellular acetylated HMGB1 (Ac-HMGB1) can activate RAGE in mesenchymal stem cells (MSCs), leading to the induction of CXCR4 expression and promoting the migration of Geminin overexpressing (Gem-OE) breast cancer cells. Moreover, the interaction between Gem-OE breast cancer cells and MSCs increases the invasiveness of triple-negative breast cancer [35]. The overexpression of Geminin is strongly linked to the proliferation and invasion of breast cancer cells, especially triple-negative breast cancer cells, a point that has been widely validated [36-38]. Therefore, blocking the Geminin-HMGB1/RAGE signaling pathway is considered a potential strategy to effectively inhibit breast cancer cell proliferation and metastasis. Especially in triple-negative breast cancer, the HMGB1/RAGE signaling pathway promotes tumor progression, whereas miR-205 can reverse this effect [23].

(2) The Role of HMGB1 in Clinical Therapy for Breast Cancer

The clinical significance of HMGB1 in breast cancer has been extensively validated, as it participates in the regulation of chemotherapy and radiotherapy in breast cancer [31, 39, 40]. Chemotherapy- and radiotherapy-induced immunogenic cell death (ICD) prompts tumor cells to release HMGB1, which is considered an immune-enhancing factor [41-43]. Kostova et al. found through immunohistochemical analysis of breast cancer samples that HMGB1 in malignant tissues showed stronger immune reactivity compared to normal tissues [44]. Thus, the expression of HMGB1 could be used as a clinical reference for treatment strategies in breast cancer.

HMGB1 plays different roles in breast cancer chemotherapy. Chemotherapy relies not only on apoptosis but also on non-apoptotic pathways, such as necrosis and autophagy, to kill cancer cells [45]. For example, Shi et al. reported that miR-129-5p enhanced the chemosensitivity of MCF-7 cells to paclitaxel by inhibiting HMGB1-mediated autophagy [26]. Liang et al. found that overexpression of miR-142-3p enhanced sensitivity to doxorubicin by negatively regulating HMGB1 and inhibiting autophagy in breast cancer cells [46]. The interaction between miRNAs and HMGB1 provides new directions for alleviating chemotherapy resistance associated with HMGB1-mediated autophagy. The ability of HMGB1-mediated autophagy to confer chemotherapy resistance in breast cancer cells has been confirmed in various conventional chemotherapy drug trials, and several new drugs have been identified that can reverse HMGB1-mediated autophagy-related chemotherapy resistance. For example, Xiaopi prescription increases breast cancer chemotherapy sensitivity by inhibiting CXCL1/HMGB1-mediated autophagy [47]. Interestingly, Zhang et al. discovered that CDK4/6 inhibitors downregulated HMGB1 expression and inhibited the TLR4/NF-κB pathway, which reversed tamoxifen resistance [48]. This indicates the potential of HMGB1 as a biomarker for identifying patients who are sensitive to CDK4/6 inhibitors. Additionally, the synergistic effect of berberine and theophylline induces HMGB1/bcl-2-mediated apoptosis, providing antitumor effects [49, 50].

Radiotherapy is a traditional treatment for various malignant tumors, including breast cancer. Although it may damage surrounding normal tissues, it significantly improves patient survival rates. Research has shown that HMGB1 enhances the radiosensitivity of breast cancer cells by exerting immunogenic effects. However, there are conflicting findings regarding the role of HMGB1 in breast cancer radiotherapy resistance. For instance, Apetoh et al. reported that ionizing radiation induces dying tumor cells to release HMGB1, which activates the TLR4/MyD88 signaling pathway in dendritic cells (DCs) and boosts the antitumor immune response [39]. Additionally, the "abscopal effect" induced by radiotherapy is a phenomenon in which tumors in non-irradiated areas also shrink. This effect is typically associated with the release of tumor antigens and exposure of damage-associated molecular patterns (DAMPs) [51]. Zhu et al. reported that after radiotherapy, breast cancer cells release HMGB1, which promotes the secretion of TNF-α by surrounding macrophages via the TLR4 pathway, thereby

enhancing the radiation-induced antitumor response [52]. However, some studies indicate a positive correlation between HMGB1 and radiotherapy resistance in breast cancer. For instance, Luo et al. discovered that HMGB1-mediated autophagy increased radiotherapy resistance in breast cancer cells, and this effect could be reversed by miR-129-5p [25].

Currently, immune therapeutic strategies targeting HMGB1 mainly focus on activating adaptive antitumor immune responses by inducing immunogenic cell death (ICD) [53]. Hubert et al. found that blocking extracellular HMGB1 can improve the breast cancer microenvironment and enhance the efficacy of anti-PD-1 immunotherapy [54]. Additionally, studies have shown that HMGB1 on the surface of TRAPs stimulates endothelial cells to upregulate PD-L1 through the TLR4-MyD88-p38/STAT3 signaling pathway, thereby inhibiting T cell function and promoting lung metastasis. Anti-PD-L1 therapy reduces lung metastasis in early-stage breast cancer mice, indicating that TRAPs and their surface HMGB1 are crucial targets for reversing immune suppression, offering a new theoretical foundation for anti-PD-L1 treatment in early breast cancer [55].

In summary, HMGB1 exhibits both tumor-promoting and antitumor effects in breast cancer. Its subcellular distribution is determined by different induction mechanisms, and these distribution patterns play a crucial role in regulating biological processes such as autophagy and immunogenic cell death, thereby affecting chemotherapy and radiotherapy outcomes in breast cancer. Furthermore, HMGB1-mediated immune activity offers new potential for immunotherapy in breast cancer, especially providing possibilities for the development of combination therapy strategies. Although HMGB1 has been proposed as a potential target for early cancer detection and treatment, its dual functions in breast cancer require further in-depth investigation.

3. The Role of S100A8 and S100A9 in Breast Cancer

The S100 gene family includes 20 members that encode low-molecular-weight calcium-binding proteins, most of which exist as homodimers, and these genes are clustered in the 1q21 region of human chromosome [56]. S100 proteins are expressed in most human malignant tumors, including breast cancer, and have been shown to be involved in regulating various biological processes such as tumor progression, metastasis, immune suppression, and treatment resistance [57]. Each S100 protein monomer consists of two helix-loop-helix motifs (EF-hands), N-terminal and C-terminal domains, and a central hinge region. The EF-hands domain can bind Ca^{2+}, and the hinge region interacts with target proteins [58, 59]. Among the S100 family, S100A8 and S100A9 are primarily expressed in myeloid cells, including monocytes, endothelial cells, and myeloid-derived suppressor cells (MDSCs). S100A8 and S100A9 form stable homodimers or heterodimers by altering their conformation and participate in the regulation of multiple signaling pathways. These signaling pathways are involved in immune homeostasis and cell metabolism, and they often undergo changes during tumor growth, driving tumor progression [60, 61].

Recently, there has been increasing attention on S100 proteins as potential prognostic biomarkers for breast cancer, and they have been shown to be closely related to the progression of inflammatory diseases, neuropathology, and various cancers [62, 63]. Clinically, high levels of S100A8 and S100A9 expression are considered to be closely associated with poor prognosis in breast cancer, especially in the basal-like subtype of triple-negative breast cancer (TNBC) [64, 65]. As a result, the potential of S100A8 and S100A9 as diagnostic and prognostic biomarkers for breast cancer has drawn extensive attention from researchers.

Traditional embroidery art still has wide application value in contemporary fashion design. For modern fashion design, it still has a very strong sound. First of all, we need to break the integrity of the design. Traditional embroidery art is often lack of abstractness, and the pattern image is very complete, but it has the characteristics of rigidity. It is not conducive to the long-term promotion of traditional ideas, and modern fashion design in the process of integration must break through the limitations of traditional embroidery, the integrity of the continuous to be broken, in order to innovate. For fashion designers, we can divide the patterns properly and pick up the relevant composition methods to make them more in line with modern people's clothing aesthetics. For example, when designing a dress, you can combine embroidery art to form a hollow way, so as to decorate the waist line and make the design effect of the whole curve more prominent. The second is to strengthen the aesthetic level of clothes and make them more in line with people's understanding of beauty. Traditional embroidery art is rooted in traditional culture, so the pattern is very exquisite and meticulous, which makes embroidery art unique and coquettish. It can enhance the aesthetic feeling of modern fashion design, so as to optimize contemporary fashion design. At present, many designers will actively try embroidery techniques in the process of design, so as to enhance the artistic value of clothing design, and even properly use embroidery techniques in foreign high-definition clothing, so as to further improve the quality of clothing.

(1)S100A8 in Breast Cancer

S100 calcium-binding protein A8 (S100A8), also known as calgranulin A or myeloid-related protein 8 (MRP8), is a member of the S100 protein family and belongs to the low-molecular-weight calcium-binding proteins [66]. Similar to other S100 family proteins, S100A8 has a helix-loop structure with charged amino acid residues, allowing it to bind divalent metal ions such as Ca^{2+} and Zn^{2+} with high affinity [67]. S100A8/calgranulin A is a damage-associated molecular pattern (DAMP) protein, primarily produced by neutrophils and monocytes, and acts as an effective chemotactic agent for phagocytic cells [68, 69]. S100A8 plays a role in multiple immune responses by binding to receptors such as TLR4, RAGE, and others, thereby activating downstream signaling pathways [70-72].

As an inflammatory response protein, S100A8 is primarily localized in the cytoplasm of cancer cells and plays a crucial role in tumor-stroma interactions [73]. The progression of breast cancer and lymph node metastasis are closely associated with the expression level of S100A8. Research has shown that in tissues from benign breast diseases, S100A8 protein expression is low or absent, while in primary breast cancer tissues, the expression of S100A8 is significantly higher than in non-metastatic breast cancer and paired metastatic lymph node tissues [74].

A study by P. Singh et al. shows that the loss of S100A8 leads to the activation of the PI3K-AKT pathway, which in turn promotes the activation of AKT2 and STAT5b, enhancing the proliferation, survival, and cell cycle progression of breast cancer epithelial cells while inhibiting

apoptosis. Furthermore, the absence of S100A8 results in the upregulation of proteins like c-jun, Glud1, and Gls, which have been recognized as markers of transformation in tumorigenesis [75].

In tumor microenvironment research, the interaction between breast cancer cells and cancer-associated fibroblasts (CAFs) promotes epithelial-mesenchymal transition (EMT), invasiveness, and tumor growth [76, 77]. Research by H. Lim and colleagues demonstrated that CAFs induce epithelial-mesenchymal transition (EMT) and enhance the invasiveness of non-malignant MCF10A breast epithelial cells by secreting interleukin-8 (IL-8). In this process, S100A8 plays a crucial role in the invasive phenotype of MCF10A cells induced by CAFs. Further research indicates that among the cytokines elevated by CAFs, IL-8 regulates the expression of S100A8 via the transcription factors p65 NF-κB and C/EBPβ. Xenograft mouse models show that co-injection of CAFs and MCF10A cells failed to induce tumor formation, while the MDA-MB-231 breast cancer cell model provided in vivo evidence of the effects of CAFs on breast cancer progression and the critical role of IL-8 in tumor growth and S100A8 expression [78]. This study reveals a new mechanism by which CAFs induce non-tumorigenic breast cells to acquire an invasive phenotype and suggests that targeting IL-8 and S100A8 may be an effective strategy for treating breast cancer.

In addition, the elevated expression of S100A8 in breast cancer cells and stromal cells has been proven to be an indicator of poor prognosis and has potential value in predicting chemotherapy response [79,80]. In clinical chemotherapy for breast cancer, high expression of S100A8 is significantly correlated with a good chemotherapy response. In a study of 120 breast cancer patients, the expression level of S100A8 was closely related to the molecular subtype and histological grade of breast cancer, and S100A8 may serve as a useful predictor of response to neoadjuvant chemotherapy (NAC) in breast cancer [80]. Further studies suggest that the E3 ubiquitin ligase Hrd1 promotes the ubiquitination of insulin-like growth factor receptor (IGF-1R) through interaction with IGF-1R, thereby reducing its expression in MDA-MB-231 and MCF7 cells. Hrd1 interacts with S100A8, promoting its degradation through the proteasomal degradation pathway. The research also discovered that the absence of S100A8 reversed the effects of Hrd1 knockdown on tamoxifen treatment, while S100A8 overexpression reversed the effects of Hrd1 upregulation on tamoxifen treatment. Therefore, Hrd1 may be a mechanism of drug resistance in breast cancer by inhibiting the expression of S100A8. In summary, S100A8 may play an anti-tumor role in breast cancer cells and is closely related to the chemoresistance of breast cancer [81].

(2) S100A9 in Breast Cancer

S100A9 expression is often upregulated in breast cancer [82-84], and its overexpression is associated with metastasis progression [85-89], chemotherapy resistance [90], and poor prognosis [65, 91, 92]. As a potential biomarker for breast cancer, S100A9 serum levels are significantly higher in breast cancer patients compared to healthy controls, and after tumor resection, S100A9 serum levels significantly decrease ($P < 0.01$), suggesting its potential in breast cancer diagnosis and prognosis follow-up [93]. Additionally, Bertolini et al. found that the absence of S100A9 prevents sEVHYP-induced breast lesions, suggesting that S100A9 may be a potential biomarker in the development of breast cancer with potential for early diagnosis and disease monitoring [94]. Additionally, a study generated S100A9−/− cells from genetically identical mouse breast cancer cell lines (highly malignant 4T1 and low malignant 67NR) and implanted them into wild-type (wt) or S100A9−/− mice (n = 10). In the experiment, anti-S100A9-Cy5.5 targeted fluorescent reflectance imaging was used for evaluation, and the results showed that tumor contrast noise was significantly reduced in S100A9−/− mice. No significant differences were observed between 4T1-ko and 67NR-ko cells compared to wild-type cells. Under anti-PD-L1 treatment, the presence of S100A9 was significantly reduced compared to the control group. This study demonstrates that S100A9-specific imaging can serve as an effective imaging biomarker for the formation and activity of the tumor microenvironment (TME) in breast cancer [95]. Therefore, researchers may further investigate and study S100A9 as a potential biomarker for breast cancer.

In terms of biological function, S100A9 has been shown to promote migration and invasion of human breast epithelial cells mediated by H-ras and enhance breast tumor recurrence through amplification of chromosome 1q21[88,96]. Furthermore, S100A9-targeted therapies (such as CPMV-G3) have shown significant efficacy in the prevention of breast cancer lung metastasis. In a mouse model of breast cancer lung metastasis, S100A9-targeted therapy resulted in a 99-fold reduction in tumor nodules, highlighting its crucial role in preventing lung metastasis of breast cancer [97]. However, some studies have found that the DNA binding inhibitor 1 (Id1) promotes breast cancer metastasis by inhibiting the expression of S100A9, suggesting that the role of S100A9 in breast cancer metastasis may be dual, requiring further investigation [98].

In breast cancer treatment, BRCA1 loss can activate S100A9 to upregulate CXCL12 and promote the activation of pStat3. The upregulated CXCL12 protein further amplifies the carcinogenic signals of S100A9. S100A9 inhibits the proliferation and function of cytotoxic T cells by recruiting and activating myeloid-derived suppressor cells (MDSCs), and through the S100A9-CXCL12 axis, it promotes the creation of a tumor-permissive microenvironment, which induces resistance of breast cancer cells to immune checkpoint blockade (ICB). This provides strong support for immune evasion in breast cancer. The use of S100A9 inhibitors (such as Tasquinimod) can restore the sensitivity of BRCA1-mutant breast cancer to immune checkpoint inhibition [99].

In breast cancer chemotherapy resistance, S100A9 often forms heterodimers with S100A8, jointly affecting resistance mechanisms. Studies have suggested that S100A9, when expressed independently, can be a potential predictive marker for distinguishing drug-resistant (DR) and drug-sensitive (DS) breast cancer patients undergoing combination chemotherapy with doxorubicin (Doxo) and docetaxel (Docetaxel). In S100A9 immunohistochemistry (IHC) testing, it exhibited a specificity of 81.8%, sensitivity of 47.4%, and a positive predictive value of 81.8% in differentiating between the drug-resistant and drug-sensitive groups. Although S100A9 offers a new approach for personalized treatment as a predictive biomarker of chemotherapy resistance, its exact mechanism of action is still not fully understood and needs further exploration [100].

(3) Sl00A8/A9 in Breast Cancer

S100A8 and S100A9 usually exhibit pro-inflammatory and anti-inflammatory properties by forming heterodimers (S100A8/A9, also known as calprotectin), which are

considered sensitive biomarkers for monitoring inflammatory activity [101, 102]. In the serum of breast cancer patients, the concentration of S100A8/A9 heterodimers is significantly higher than in healthy individuals, and it is positively correlated with tumor size, making it a potential diagnostic and prognostic indicator for breast cancer [103].

S100A8/A9, as a damage-associated molecular pattern (DAMP), activates pro-inflammatory responses and regulates carcinogenic signals by binding to cell surface receptors, such as the receptor for advanced glycation end products (RAGE) [104-106]. RAGE is considered the main receptor for S100A8/A9, and binding to it activates downstream signaling pathways [107, 108]. The interaction between S100A8/A9 and RAGE is particularly important in triple-negative breast cancer (TNBC), as its expression is upregulated in invasive and metastatic TNBC and is associated with poor prognosis [109]. S100A8/A9 promotes epithelial-mesenchymal transition (EMT) in TNBC cells and lung metastasis in xenograft mouse models through RAGE [110]. Recent studies have found that the S100A8/A9-RAGE system stimulates the growth and migration of TNBC cells by promoting FAK phosphorylation and regulating the Hippo pathway, which increases YAP nuclear localization and transcriptional activity [111]. Additionally, S100A8/A9 stimulates ETV4 activation and regulates ZEB1 through extracellular binding to the MCAM receptor, resulting in aggressive metastatic spread of breast cancer to the lungs, thus enhancing tumor invasiveness [112].

In the treatment of breast cancer, the mRNA expression levels of S100A8/A9 in HR-/HER2+ primary breast tumors are strongly correlated with the HER2 pathological status, and in HR-/HER2+ breast cancer, the expression of S100A8/A9 is highest and closely associated with STAT3 phosphorylation. Ruxolitinib, as a JAK1/2 inhibitor, can disrupt the IL-6-JAK2-STAT3-S100A8/A9 signaling pathway, thereby inhibiting the tumorigenicity of HR-/HER2+ breast cancer [113]. However, the combination of Ruxolitinib and trastuzumab failed to improve the progression-free survival (PFS) in patients with trastuzumab-resistant metastatic HER2+ breast cancer [114].

In breast cancer anti-angiogenic therapy, myeloid-derived suppressor cells (MDSCs) are considered a key target to overcome resistance to anti-angiogenic treatment. Liposomal doxorubicin and liposomal vaccines containing the E75 immunogenic peptide can significantly reduce the levels of MDSCs, as well as S100A8 and S100A9 expression in breast tumor mice [115]. Additionally, DOX treatment-induced IL-13R+ miR-126a+ MDSCs (DOX-MDSCs) can promote lung metastasis of breast tumors, while miR-126a promotes angiogenesis, and S100A8/A9 mediates the apoptosis of MDSCs. Blocking the miR-126a pathway may provide a new option for targeted therapy [116].

In terms of chemotherapy resistance, studies have found that mRNA expression of S100A8 and S100A9 is elevated in Her2+/basal-like breast cancer, which is negatively correlated with the expression of ESR1 and GATA3. The enhanced expression of S100A8/A9 in the breast cancer microenvironment may be related to the loss of estrogen receptors (ER), which leads to reduced sensitivity of breast cancer cells to endocrine therapy [91]. Moreover, the CXCL1/2-S100A8/A9 loop functions as a cancer cell survival axis connecting chemotherapy resistance and metastasis in breast cancer. Under chemotherapy activation, S100A8/A9 secretion increases, further aggravating resistance to cyclophosphamide and doxorubicin [90]. Additionally, S100A8 and S100A9 enhance chemotherapy resistance in breast cancer cells by activating the pro-survival ERK1/2 and ribosomal protein S6 kinase β1 pathways [117].

In summary, as important members of the S100 protein family, S100A8 and S100A9 may play a dual role in breast cancer, contributing critically to metastasis, invasion, and drug resistance, thereby providing potential new targets for breast cancer therapy.

4. The Role of IL-33 in Breast Cancer

Interleukin-33 (IL-33) is an alarmin in the IL-1 family, which is constitutively expressed on the surface of epithelial barriers. When tissues undergo compression, injury, or necrosis, IL-33 is released into the extracellular space, where it acts through its receptor ST2 to initiate the subsequent inflammatory response [118-123]. In recent years, the role of IL-33 in tumorigenesis has attracted increasing attention. Research indicates that IL-33 is closely linked to multiple cancers, with increased expression observed in colorectal cancer (CRC) tissues, breast cancer, and serum of non-small cell lung cancer (NSCLC) patients [124-126]. In breast cancer studies, IL-33 and ST2 have been found to be expressed in both normal breast cells (MCF10A) and breast cancer cell lines, such as BT-474, MDA-MB231, MCF7, and SK-BR3[127].

High expression levels of IL-33 or ST2 may be important indicators of poor cancer prognosis and are positively correlated with advanced stages of the disease [128-133]. A study demonstrated an active immunization strategy based on presenting mature IL-33 molecules on the surface of recombinant virus-like particles (VLPs), which can continuously inhibit dysfunctional IL-33 signaling, thus improving the tumor immune microenvironment. Vaccination with HBcAg-33 VLP can trigger a strong anti-IL-33 antibody response, inhibiting the growth of orthotopic 4T1 breast tumors. IL-33-targeted immunotherapy downregulates Th2 responses and enhances Th1/CTL responses, promoting the generation of anti-tumor effector cells, while also altering the immunosuppressive tumor microenvironment by inhibiting MDSCs and Tregs, promoting effector cell accumulation and maintaining tumor tissue [134]. It is noteworthy that blocking endogenous overexpression of IL-33 in 4T1 tumor-bearing mice produced results that were significantly different from those in the 4T1 tumor model established by Gao et al. through IL-33 overexpression. In Gao's study, IL-33 overexpressed by tumor cells primarily acts as an alarmin, triggering the immune system and enhancing responses from dendritic cells (DCs), natural killer (NK) cells, and Th1/CTL cells, which aids in clearing tumor cells and generating marked anti-tumor effects [135, 136].

IL-33, as a ligand for ST2, is released into the extracellular space, where it binds to ST2 on the surface of immune cells like innate lymphoid cells, mast cells, activated T cells, and eosinophils, triggering the production of inflammatory mediators [137]. In contrast, neutralizing or gene deletion of the ST2 receptor has been shown to inhibit breast cancer metastasis, suggesting that IL-33 signaling contributes to the accumulation of immunosuppressive cells [138, 139]. Research has shown that serum sST2 levels are significantly increased in breast cancer patients and are closely associated with tumor metastasis. Additionally, serum VEGF levels in breast cancer patients are also significantly elevated and positively correlated with IL-33 and sST2 levels, suggesting

that increased IL-33 concentration may be an important indicator of poor prognosis in breast cancer [140]. Further studies have shown that deletion of the IL-33/ST2 signaling pathway can significantly delay primary tumor growth and inhibit metastasis. In ST2-/- mice, primary tumor growth is slower, and the formation and growth of metastases are inhibited. By day 36, the incidence of lung and liver metastasis in ST2-deficient mice was significantly lower compared to wild-type mice, and the number and size of metastatic nodules were notably reduced [138]. Moreover, IL-33 also mediates eosinophil involvement in the endogenous immune response of breast cancer through its receptor ST2[141]. The measurement of IL-33 and its receptor sST2 levels also has important applications in the differential diagnosis between idiopathic granulomatous mastitis (IGM) and breast cancer [142].

In breast cancer progression, IL-33 promotes tumor growth by activating the JNK/cJun, MEK/ERK, and STAT3 signaling pathways, stimulating epithelial cell proliferation [127]. Additionally, studies have found that IL-33 expression is regulated by the activity of SP1 and FOXA1 transcription factors, with increased SP1 and FOXA1 activity leading to elevated IL-33 levels and promoting tumor progression [143]. In chemotherapy resistance in breast cancer, high expression of IL-33 is associated with resistance of breast cancer cells to tamoxifen, stimulating the emergence of stem cell-like tumor characteristics [144]. Therefore, the role of IL-33 in breast cancer involves not only tumor immune evasion but also a close association with chemotherapy resistance.

5. Conclusion and Perspectives

This review emphasizes the critical role of alarmins (HMGB1, S100A8, S100A9, and IL-33) in the initiation, progression, and treatment of breast cancer. And they exert multiple biological functions in the immune microenvironment of breast cancer. These alarmins not only play significant roles in promoting the proliferation, invasion, and metastasis of tumor cells but are also closely related to resistance in clinical treatment. The differential functions of HMGB1 in various subcellular locations highlight its complex regulatory mechanisms in the tumor microenvironment, whereas S100A8 and S100A9 demonstrate notable pro-inflammatory and drug resistance effects in triple-negative breast cancer. The dual role of IL-33 shows its potential in promoting immune suppression and activating anti-tumor immune responses. Although the roles of alarmins in breast cancer have been extensively studied, their specific mechanisms in regulating the tumor microenvironment and responding to treatment need further exploration.

Future research should focus on the specific mechanisms of alarmins in immune evasion and treatment response in breast cancer. In the exploration of these mechanisms, strengths should be maximized and weaknesses minimized, with in-depth studies on their inhibitory roles in breast cancer and suppression of their promoting effects, to improve patient prognosis through targeted therapy. These findings provide possibilities for the development of new immunotherapeutic strategies, which are expected to bring better outcomes and more options for the clinical treatment of breast cancer.

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