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REVIEW

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Unravelling the role of ubiquitin-specific proteases in breast carcinoma: insights into tumour progression and immune microenvironment modulation

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Abstract

Breast cancer is a prevalent malignancy worldwide, and its treatment has increasingly shifted towards precision medicine, with immunotherapy emerging as a key therapeutic strategy. Deubiquitination, an essential epigenetic modification, is regulated by deubiquitinating enzymes (DUBs) and plays a critical role in immune function and tumor progression. Ubiquitin-specific proteases (USPs), a prominent subgroup of DUBs, are involved in regulating immune cell functions, antigen processing, and T cell development in the context of breast cancer. Certain USPs also modulate the differentiation of immune cells, such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), within the breast cancer immune microenvironment. Furthermore, several USPs influence the expression of PD-L1, thus affecting the efficacy of immune checkpoint inhibitors. The overexpression of USPs may promote immune evasion, contributing to the development of treatment resistance. This review elucidates the role of USPs in modulating the immune microenvironment and immune responses in breast cancer. Additionally, it discusses effective strategies for combining USP inhibitors with other therapeutic agents to enhance treatment outcomes. Therefore, targeting USPs presents the potential to enhance the efficacy of immunotherapy and overcome drug resistance, offering a more effective treatment strategy for breast cancer patients.

Keywords Breast carcinoma, Ubiquitin-specific proteases, Immune response, Immune microenvironment, PD-L1, Tumour microenvironment

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Background

The incidence of breast cancer is currently increasing, particularly among younger individuals, surpassing lung cancer as the most prevalent form of cancer worldwide [1]. Currently, breast cancer accounts for one-eighth of all cancer cases and has been the most common malignant disease in women since 2020 [2]. The primary treatment modalities for breast cancer include surgical procedures, adjuvant therapy, and comprehensive treatment. Adjuvant therapy encompasses radiation therapy, chemotherapy, and endocrine therapy, whereas comprehensive treatment involves the combined use of two or more of these approaches. In recent years, novel treatment modalities for breast cancer, including immunotherapy and gene-targeting therapy, have emerged. It is generally believed that the development and progression of breast cancer are not influenced by immune surveillance. However, the identification of tumour-infiltrating lymphocytes (TILs) indicates the presence of immune infiltration in breast cancer, stimulating extensive research into the immunological aspects of breast cancer [3, 4]. This has laid a foundation for the application of immune medications in the treatment of breast cancer, expanding their potential applications. Notably, compared with HR-positive (HR+) breast cancer patients, HER2 + and triple-negative breast cancer patients present varying numbers of TILs, and the number of TILs is significantly greater in these patients [5]. Tumor-infiltrating lymphocytes (TILs) play a crucial role not only in mediating the immune response, including both attacks and suppression of Th1 cells, but also in their interactions with tumor cells, which consequently influences the immune microenvironment [6]. For instance, USP43 modulates the infiltration of immune cells surrounding pancreatic ductal adenocarcinoma, thereby affecting patient prognosis [7]. In recent years, USPs have emerged as promising targets for inhibiting tumor formation and progression, with more than 40 USPs identified as directly or indirectly involved in tumor development and treatment [8]. This review aims to summarize the impact of USPs on the immune microenvironment and immune responses in breast cancer while discussing effective strategies for combining USP inhibitors with other pharmacological agents to enhance therapeutic outcomes. Ultimately, this review seeks to provide new insights for improving breast cancer treatment.

Immune microenvironment of breast cancer

The immune microenvironment of breast cancer consists of infiltrating cells and their secreted active mediators (Fig. 1). Along with the tumour-killing effect mediated by T lymphocytes in specific antitumour immune responses, nonspecific immune responses mediated by NK cells, dendritic cells, myeloid-derived suppressor cells (MDSCs), ILs, chemokines, and TNF-α constitute the first line of defence in antitumour immunity, which helps eliminate tumour cells and inhibits their proliferation [9, 10]. The lymphocytes involved in breast cancer immune surveillance include type 1 helper T cells (Th1), CD8 + cytotoxic T lymphocytes (CTLs), M1 macrophages, N1 neutrophils, and dendritic cells (DCs). Conversely, M2 macrophages, MDSCs, N2 neutrophils, and Tregs play a role in negatively regulating the immune process, inhibiting immune responses, and further promoting the development of tumour cells [11]. Some USPs play crucial roles in regulating the activation and function of immune cells, thereby altering the tumour immune microenvironment and even promoting immune escape. USP15 is a key regulatory factor in T-cell activation [12]. USP1 regulates the differentiation of CD4 + T cells and Th17 cells [13]. Ablation of USP5 in CD8 + T cells increases the production of cytokines and cytotoxic molecules [14]. Exosomal circUSP7 inhibits the secretion of cytokines by CD8 + T cells, thereby suppressing tumour cell growth and leading to immune escape [15]. Some studies suggest that tumour-infiltrating lymphocytes (TILs) indicate a favourable prognosis for patients with breast cancer and can also predict treatment outcomes [16]. In the immune environment, CD4 + helper T cells play a positive regulatory role in the antigen presentation process. USP12 activates CD4 + T-cell responses, which can secrete specific cytokines and activate antigen-presenting cells [17].

Tumour-associated macrophages (TAMs) and MDSCs

TAMs are mainly divided into M1 and M2 types. In the tumour microenvironment (TME), M2 macrophages promote the development of tumours [18]. Breast cancer cells can secrete factors that induce macrophages to undergo M2 polarization. In turn, the cytokines and growth factors secreted by M2 macrophages regulate processes such as the proliferation, invasion, migration, and angiogenesis of tumour cells [19, 20]. M2 macrophages also release immunosuppressive factors that can downregulate the metabolism and function of T cells. Additionally, M2 macrophages can promote the aggregation of regulatory T cells (Tregs), thereby enhancing their immunosuppressive function [21, 22]. An increase in the number of CD163 + M2 macrophages suggests that breast tumour cells may exhibit increased proliferation and a low degree of differentiation [23]. In contrast, in the antitumour immune reaction process, the presence of more M1 macrophages and CD8 + T cells increases the quantity of tumour-infiltrating cells, the immune reaction capacity of T-cell subpopulations, and the ability to disrupt the peripheral tolerance of CD4 + T cells. Moreover, the role of M2 macrophages is opposite to that of M1 macrophages [24]. Exosome-derived circ-0100519

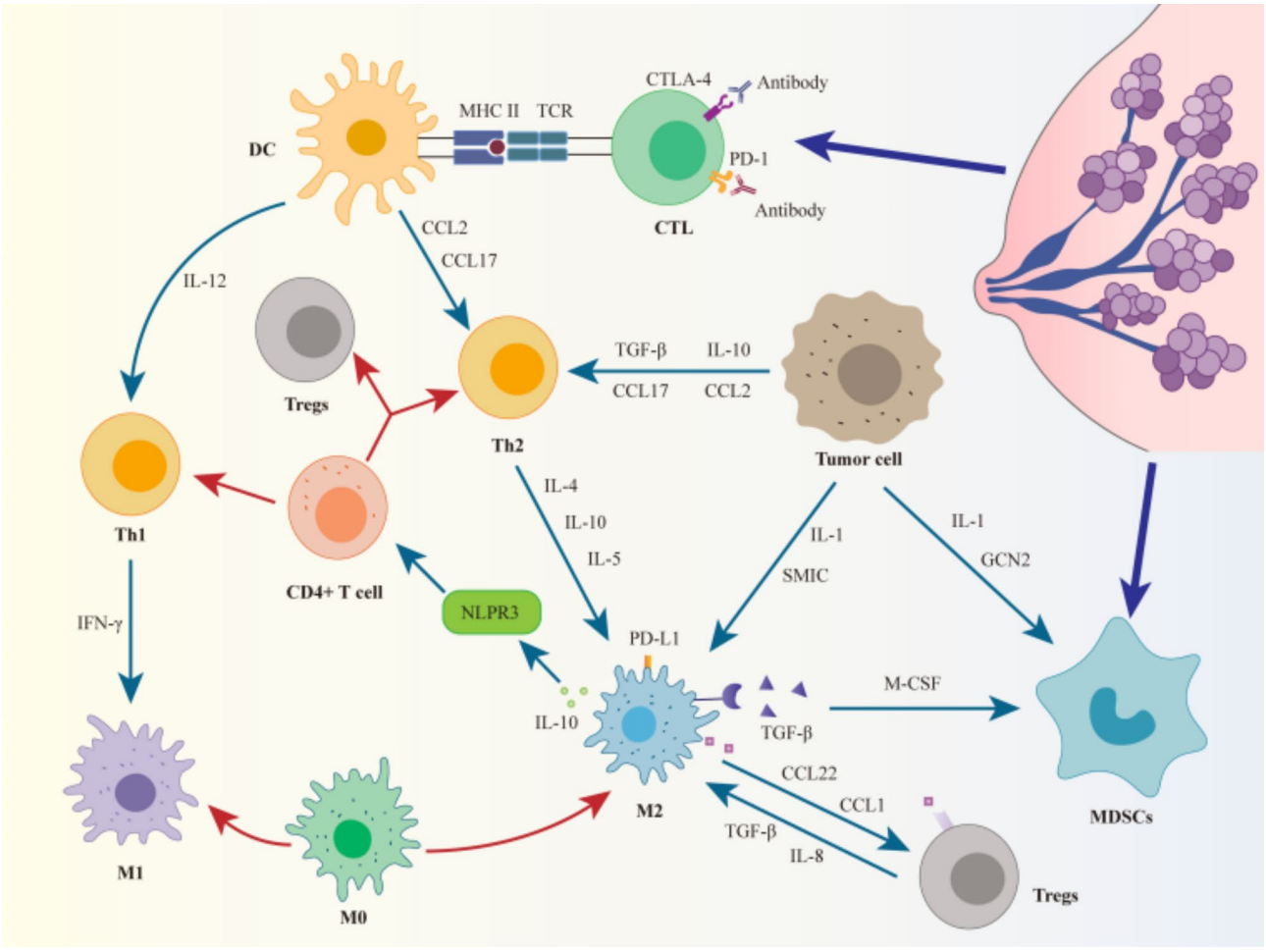

Fig. 1 Breast cancer immune microenvironment: cells involved and their secreted Cytokines

induces M2 macrophage polarization and promotes breast cancer progression via the USP7/NRF2 axis [25]. The expression of USP12 is negatively correlated with that of tumour-associated macrophages and PD-L1, and it is also one of the key regulatory factors of CD4 + T cells. In breast cancer, tumour-associated macrophages, PD-L1, and CD4 + T cells are involved in the tumour immune microenvironment [26]. Therefore, it is speculated that USP12 may also be involved in regulating the immune microenvironment of breast cancer, but further research is needed to verify this.

The growth and proliferation of tumours are tightly related to MDSCs, which play an inhibitory role in immunotherapy [27]. In breast cancer, cancer cells can recruit MDSCs, which counteract the antitumour effects of T cells and B cells in the TME. This further suppresses antitumour reactions and promotes the formation of a protumor microenvironment [28]. Like TAMs, MDSCs produce vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), and matrix metalloproteinase 9 (MMP9), which contribute to the remodelling of the TME. Additionally, they can induce immune tolerance, thereby promoting breast cancer progression and metastasis [29]. Some relevant clinical investigations have shown that the circulating levels of MDSCs influence the stage of breast cancer [30]. TAMs stimulate the upregulation of IL-10 expression in MDSCs, leading to the downregulation of IL-12 secretion in macrophages, creating a self-perpetuating negative feedback loop that impairs effector T-cell function [31]. Additionally, MDSCs support cancer progression by lowering the production of regulatory T cells (Tregs) and Th17 cells, thereby altering the tumour-promoting microenvironment to drive immune evasion [32].

Regulatory cells

In the immune system, Tregs play an inhibitory role and are involved in the development of tumour immune tolerance. Owing to their negative regulation of immunity, the accumulation of Tregs affects the long-term prognosis of breast cancer patients and is likely to lead to immune escape [33, 34]. During the migration of Tregs to the site

of tumour occurrence, chemokines secreted by breast cancer cells bind to their surface receptors, where they participate in regulating this process. Moreover, various soluble factors released by infiltrating Tregs hinder the proliferation of effector cells and cytotoxic T cells in the TME. Hence, they facilitate tumour metastasis and phenotypic development [35]. The key regulatory molecule of Tregs is forehead box protein P3 (Foxp3), which is part of the forehead/winged helix transcription factor family. Foxp3 reshapes the TME, maintaining an immunosuppressive state and promoting immune escape [36]. USP7 deubiquitination stabilizes Foxp3, thereby enhancing the immunosuppressive function of Treg cells to promote tumour growth [37]. USP44 and USP7 have synergistic effects, and their co-overexpression almost completely eliminates the polyubiquitination of Foxp3 [38]. USP21 regulates the stability of the Foxp3 protein at the posttranslational modification level [39], and USP22 influences Treg function by increasing the level of Foxp3 [40]. USP1 promotes the proteasomal degradation of Foxp3 [13]. In the TME, highly expressed Foxp3 in Tregs acts as a transcriptional activator of CCR4, reducing immune reactivity against tumours and promoting tumour progression [36]. In vitro experimental results have shown that, under the action of this chemokine, tumour-associated macrophages (TAMs) secrete various chemokines, including CXCL1, further improving the differentiation and immunosuppressive ability of Treg cells [41]. Inhibiting TAM/CXCL1 activity in the TME has been shown to significantly suppress immune evasion and migration in breast cancer by influencing the function of Tregs in relevant studies [41].

PD-1 and PD-L1

After binding with PD-L1, PD-1 negatively regulates the immune system, reducing T-cell proliferation, downregulating cytotoxic activity, and increasing the number of Tregs in the TME [6]. These mechanisms enable tumours to evade immune reactions [42]. The immune checkpoint receptor PD-1 can influence the activity of T cells, thus regulating the body's immune suppression process. When they bind together, they lead to the deubiquitination of the downstream protein kinases SYK and PI3K, further restraining the expression of genes necessary for controlling T-cell activity and cytokine transcription translation [43]. Overexpression of PD-L1 inhibits the cytotoxic capability of T cells, further promoting immune evasion in tumours [44]. In the TME, PD-L1 is derived primarily from TAMs [18]. Tumour-associated macrophages can secrete tumour necrosis factor (TNF-α) and interleukin-1 beta (IL-1β). In the presence of these two secreted factors, the expression of PD-L1 increases [45]. The expression level of PD-L1 in tumour cells can be achieved through the activation of the NF-κB signalling pathway by TNF-α and IL-1β [46]. USP5 positively regulates the stability of the PD-1 protein at the posttranslational level [14]. USP8 regulates the protein stability of PD-L1, affecting the immune escape of tumours [47]. Different types of regulatory T cells (Tregs) exist in different locations. One type is thymus-derived Tregs (tTregs), which originate from the thymus. The other type is peripherally induced Tregs (pTregs), which develop outside the thymus in peripheral lymphoid tissues and nonlymphoid tissues and are also known as induced Tregs (iTregs) [48]. PD-L1 can promote the expansion of pTregs in the TME, thereby suppressing the response of T cells to cancer [49]. Research indicates that the PD-L1 pathway can increase the degree of differentiation of peripheral Tregs (pTregs) [49]. IFN-γ has the strongest ability to increase PD-L1 expression [50]. The secretion of IFN-γ can also be regulated by pathways related to tumour-associated macrophages [27].

Ubiquitin-specific protease family

Ubiquitination is a reversible posttranslational modification process that involves the adhesion of ubiquitin molecules to proteins of interest. This process forms an isopeptide bond between the C-terminal carboxyl group of ubiquitin and the lysine amino group of the target protein, facilitated by the E1 (ubiquitin-activating enzyme), E2 (ubiquitin-conjugating enzyme), and E3 (ubiquitin ligase) enzyme families. Ubiquitination is critical for various physiological processes, such as protein degradation, DNA damage and repair, the cell cycle, and immune reactions [51]. The deubiquitination process, which is mediated by deubiquitinating enzymes, is a protein modification that ensures the normal progression of physiological processes. USPs constitute the maximal subclass of deubiquitinating enzymes, and more than 80% of protein degradation processes in eukaryotic cells require the involvement of USPs. All USPs share a USP domain consisting of three subdomains resembling a right-hand thumb, palm, and fingers. The finger subdomain interacts with the distal ubiquitin molecule, whereas the palm and thumb subdomains catalyse the interaction between the palm and thumb subdomains. Overall, ubiquitination and deubiquitination processes and enzymes play essential roles in regulating cellular functions (Fig. 2). Dysregulation of these segments can lead to tumour occurrence and progression.

Ubiquitin-specific proteases in the breast cancer immune microenvironment

USP7

USP7 is a cysteine protease consisting of 1102 amino acid residues. USP7 contains multiple domains, including an N-terminal domain rich in polyglutamine, that have the ability to bind to various proteins. It also has a catalytic

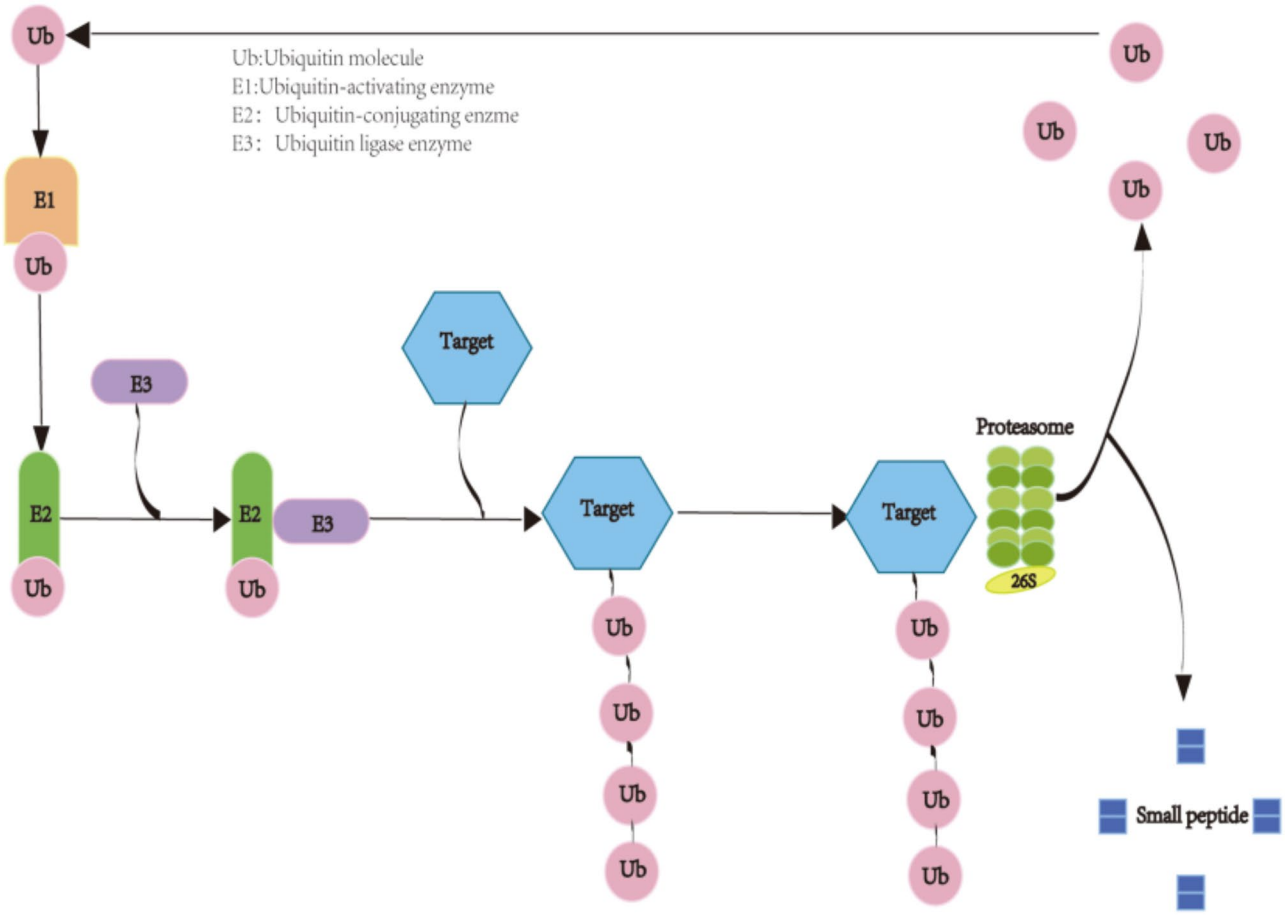

Fig. 2 The structure of ubiquitin proteases and the ubiquitination modification process

domain with fingers, thumbs, and finger base motifs, which are involved in its enzymatic activity as a protease. Additionally, USP7 possesses a C-terminal ubiquitin-like (UBL) domain. USP7 is involved in key growth and homeostatic processes, such as cell lifecycle regulation, localization, immune reactions, transcription factor activity, and epigenetic activity [52].

The growth of regulatory T (Treg) cells cannot occur without stable expression of Foxp3 [40]. USP7 is a nucleus-localized deubiquitinase that interacts with Foxp3 and exhibits activity in both nTreg and iTreg cells, leading to the deubiquitination of Foxp3. USP7 expression is upregulated in Treg cells, and USP7 deubiquitinates Treg cells by interacting with Foxp3, leading to an increase in the quantity of the Foxp3 protein. Knockdown of USP7 in Treg cells results in reduced Foxp3 protein levels and weakens the ability of Treg cells to suppress effector T cells [53]. Research indicates that USP7-mediated deubiquitination stabilizes Foxp3 and Tip60, enhancing the immunosuppressive influence of Treg cells to accelerate tumour growth [37]. Furthermore, exosomal circ-0100519 induces M2 macrophage polarization and promotes breast cancer progression through the USP7/NRF2 axis [25].

USP8

The microtubule interacting and trafficking (MIT) domain, the rhodanese-like domain (Rhod), the SH3 binding motif (SBM), the 14-3-3 binding motif (14-3-3BM), and the deubiquitin acid catalytic domain (DUB) collectively constitute USP8. Ubiquitin molecules on target proteins are removed by deubiquitinating domains through deubiquitination [54]. USP8 modulates the T-cell receptor (TCR) signalling complex and participates in the regulation of immune processes, mainly exerting its crucial role in adjusting endocytosis and protein transport by regulating deubiquitination activity in the endosomal sorting complex required for transport (ESCRT) [47]. Overexpression or functional mutation of USP8 can support the regulatory function of T cells but inhibits the effect of CD8 + T cells, contributing to tumour progression and immune escape [55].

USP8 activates the TGF-β/SMAD signaling pathway, which can EMT, tumor cell diffusion, and metastasis. USP8 further enhances these TGF-β/SMAD-induced

processes. Inhibiting USP8 impairs TGF-β/SMAD signal transduction, leading to reduced stability of the β receptor II (βRII) and a decreased quantity of TβRII + circulating extracellular vesicles (crEVs), which in turn diminishes CD8 + T-cell exhaustion and reinstates antitumor responses [56]. Additionally, USP8 plays a role in protein degradation, maintaining the stability of programmed death-ligand 1 (PD-L1) and influencing immune evasion in cancers [57]. Tumor necrosis factor receptor-associated factor 6 (TRAF6) acts as a dual regulator of immune cell signaling, significantly influencing the progression, function, and pathogenesis of the immune microenvironment. Furthermore, TRAF6 functions as a RING finger domain E3 ubiquitin ligase. Upon recognizing PD-L1, USP8 regulates its degradation by removing ubiquitin substrates attached via K63 linkages. Inhibition of USP8 predominantly counteracts K48-linked ubiquitination and PD-L1 degradation by enhancing TRAF6-mediated K63-linked ubiquitination, thereby increasing PD-L1 levels [47]. Moreover, USP8 inhibition triggers innate immune responses by activating TRAF6-NF-κB signaling, interferon type I signaling, and MHC-I expression, potentially mitigating the adverse effects of PD-L1 and shaping TME. The transcription factor FOXO1 promotes thymocyte maturation and enhances the expression of genes encoded by the cytokine receptor IL-7Rα, with USP8 being crucial for this process. USP8 also facilitates normal T-cell homeostasis by increasing IL-7R release mediated by FOXO1, which is essential for T-cell receptor (TCR) activation [58].

USP12

USP12, located on chromosome 13q12.13, is a micromolecular protein comprising 370 amino acid residues. Notably, the external rim of the finger domain of USP12 features a unique helical structure referred to as the "little finger", which is distinct from typical USP structures as it is separated from the other finger domains. This characteristic suggests that the finger domain of USP12 possesses considerable structural flexibility [59]. Research has demonstrated that USP12 plays a critical role in reprogramming the tumor microenvironment. NF-κB is involved in regulating genes associated with T-cell survival, proliferation, and effector functions, as well as in the transcription of T-cell receptor (TCR) channels. USP12 primarily modulates the activation and phenotype of T cells by regulating B-cell lymphoma 10 (BCL10). Specifically, USP12 deubiquitinates BCL10, maintaining its stability and activating the NF-κB pathway to stimulate CD4 + T-cell responses. Additionally, the BCL10-mediated NF-κB signaling pathway restricts cell activation, proliferation, and the production of downstream cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). USP12 regulates this process through its interaction with BCL10. Furthermore, USP12 exerts a positive regulatory effect within cells and modulates T-helper 1 (Th1) and Th17 cells through intrinsic mechanisms [17]. The substrate of USP12, protein phosphatase magnesium-dependent 1B (PPM1B), acts as a phosphatase for IκB kinase β (IKKβ); thus, downregulation of USP12 can accelerate PPM1B ubiquitination and degradation, promoting NF-κB activation and influencing the immune microenvironment. Additionally, USP12 regulates chemokine production by inhibiting NF-κB signaling activity [60]. Chemokines CXCL1 and CXCL8, regulated by USP12, share the receptor CXCR2, which serves as a potent chemoattractant for recruiting tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). Moreover, chemokine CCL2 facilitates the recruitment and polarization of tumor-infiltrating myeloid cells, a process also downregulated by USP12. Overexpression of USP12 inhibits tumor growth and alters TME components, while CXCL1 and CCL2 can mitigate this effect. The PI3K-AKT-mTOR pathway can elevate PD-L1 levels in tumor cells; however, its overactivation leads to decreased USP12 expression. Consequently, silencing USP12 results in increased PD-L1 expression in tumor cells [61]. Research indicates that USP12 is a positive regulator of mononuclear MDSCs. The absence of USP12 reduces the infiltration of mononuclear (M)-MDSCs and impairs their suppressive function, leading to enhanced CD8 + T-cell responses and reduced tumor growth [60].

USP15

The catalytic domain of USP15 is a typical USP fold with an additional N-terminal DUSP domain and a ubiquitin-like (UBL) domain. The catalytic domain includes the finger, palm, and thumb regions. The DUSP domain is a tripod-like structure similar to AB3, composed of a bundle formed by three α-helices that support three strands of antiparallel β-sheets. It consists of approximately 90 amino acid residues. Moreover, the UBL domain is made up of approximately 80 residues, forming a β-grasp fold [62].

Ten-eleven translocation (TET) enzymes are dioxygenases that depend on α-ketoglutarate (α-KG) and iron (Fe^{2+}) for their catalytic activity. TET2, a member of the TET family, plays a crucial role in regulating DNA demethylation. USP15 acts as a deubiquitinase inhibitor of TET2, with K1299 identified as the primary site for TET2 monoubiquitination. This positions USP15 as the principal deubiquitinase for TET2 at the K1299 site. Among the substrates of USP12, IκBα and TRIM25, which are E3 ligases, directly participate in immune responses and interferon (IFN) signaling pathways, thus underscoring the significance of USP15 in innate immunity and inflammatory reactions. Furthermore, TET2 has

been shown to promote the production of chemokines in response to IFN-γ, highlighting the intricate interplay among these molecules within the immune system [63]. USP15 also regulates tumor immunity-related pathways, including the TGF-β signaling pathway [64]. It stabilizes the TGF-β receptor and the downstream signaling molecule R-SMAD, thereby enhancing TGF-β activity. Additionally, USP15 can deubiquitinate the E3 ligase SMURF2. By restraining the interaction between TGF-β-activated kinase 1 (TAK1) and its binding proteins TAB2 and TAB3, USP15 increases the stability and activation of TGF-β and its downstream pathways, leading to enhanced NF-κB activation [65]. NF-κB regulation involves numerous genes implicated in innate and adaptive immune responses, with key downstream signaling steps including the hydrolysis of IκBα protein and NF-κB nuclear translocation, processes that are negatively regulated by USP15 via K48-linked ubiquitination of IκBα. Targeting USP15 can induce apoptosis in tumor cells while enhancing anti-tumor T-cell responses. Through its deubiquitinase function, USP15 stabilizes MDM2, mediates the ubiquitin-dependent degradation of NFATc2, restrains T-cell viability, and negatively regulates the production of T-cell cytokines [66]. Additionally, USP15 can promote T-cell activation [6]. Moreover, USP15 plays an intrinsic role in regulating T-cell function in response to the MCA and primary tumor formation. A deficiency in USP15 contributes to increased IFN-γ production and the formation of an immunosuppressive environment. VGLL4 inhibits PD-L1 transcription by suppressing STAT3 activation, which enhances the efficacy of anti-PD-L1 antibody immunotherapy for triple-negative breast cancer. As a deubiquitinase of VGLL4, USP15 is involved in the regulation of PD-1 through VGLL4. Deficiency in USP15 leads to the overactivation of IFN-γ-producing T cells, ultimately resulting in the upregulation of PD-L1 and CXCL12 expression and increasing the recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which further contributes to the development of an immunosuppressive environment [67].

USP21/22

Compared with most DUBs, USP21 has a relatively simple structure composed of only one N-terminal zinc finger and one C-terminal catalytic domain. The N-terminal region of USP21 is inherently disordered [68]. Unlike other deubiquitinating enzymes, the N-terminal zinc finger of USP22 lacks a ubiquitin tail-binding pocket; thus, it does not directly interact with ubiquitin. It interacts with components of the Spt-Ada-Gcn5-acetyltransferase (SAGA) complex, including SAGA-associated factor 73 (ATXN7/Sgf73), ATXN7L3/Sgf11, and ENY2/transcriptional coactivator and sugar isomerase 1 (ENY2/Sus1), forming a closely binding tetrameric deubiquitinase module within the SAGA complex (DUBm) that deubiquitinates target proteins [69].

USP22 closely participates in cellular processes related to tumour development, such as cell multiplication, apoptosis, diffusion, metastasis, and the immune response [70]. USP22 regulates the occurrence, growth, and phenotypic modulation of T cells and B cells in normal tissues and can also alter the immune microenvironment in tumour tissues. USP21 is the most overexpressed deubiquitinase in triple-negative breast cancer and maintains the stability of the Foxp3 protein after translation. Regulatory T cells (Tregs) primarily exert immunosuppressive effects on the immune system through the expression of Foxp3. USP22 influences Treg function by increasing Foxp3 levels [40]. Lack of USP22 reduces Foxp3 stability, impairing the suppressive function of Tregs and reducing their ability to inhibit cytotoxic CD8 + T cells. Foxp3 acts as a significant target of USP21 in Treg cells. USP21 stabilizes Foxp3 through deubiquitination, preventing exhaustion of the Foxp3 protein in Treg cells [39]. NFATc2 is a regulatory molecule in T-cell activation, and USP22 promotes interleukin-2 expression in T cells by deubiquitinating and maintaining the stability of NFATc2. These findings indicate that, in the control of the T-cell immune reaction, USP22 is a positive regulator of NFATc2 [71]. USP22 also has an impact on the TME, leading to an obvious reduction in MDSCs, thereby promoting the infiltration of T cells and NK cells. Moreover, USP22 depletion enhances T-cell-mediated cytotoxicity; therefore, the levels of USP22 induce resistance to immune medications [72]. Therefore, USP22 may also be involved in regulating the immune microenvironment in breast cancer.

The PD-1 (CD279)/PD-L1 (CD274) axis is known as an "adaptive immune mechanism" that evades antitumour responses and is one of the main targets of cancer immunotherapy. Overexpressing Prdm1 inhibits the tumour immune-related response by increasing PD-L1 levels. Research indicates that the PRDM1-USP22-SPI1 axis is involved in the regulation of PD-L1 expression through the mechanism whereby SPI1 acts as a downstream effector of PRDM1, directly binds to the PD-L1 promoter, enhances its expression, and ultimately leads to the depletion of infiltrating cells [73]. USP22 deubiquitinates SPI1 and enhances its stability, thereby regulating PD-L1 expression. USP22 can also stabilize CD274 in a CDK4-independent manner. By modulating the stability of the CD274 protein by its deubiquitinase activity, USP22 prevents the proteasomal degradation of CD274 [74]. Furthermore, when the PD-L1 protein is depleted, USP22 deubiquitinates CSN5 and controls the level of PD-L1 protein through the USP22-CSN5-PD-L1 axis, thereby strengthening antitumour immune reactions [75]. The

overexpression of USP21 significantly increases PD-L1 abundance, whereas its knockdown induces PD-L1 degradation [76].

USP44

The USP44 gene is located on human chromosome 12 and consists of ZnF-UBP and USP domains. Its open reading frame (ORF) spans 2139 base pairs and encodes 712 amino acids. The catalytic domain of USP44 includes a Cys box, an Asp motif, and a His box, resembling those present in other family members, each bearing highly conserved cysteine, aspartate, and histidine residues, respectively. Moreover, it contains a centrally positioned, extensively conserved protein-binding domain closely linked to the subcellular localization of USP44 and its preventive role in chromosomal lagging [77].

As mentioned earlier, the growth and immune homeostasis of Tregs are inseparable from the regulation of Foxp3, and USP44 can interact with Foxp3. USP44 binds to Foxp3 through a ZF-proline-rich domain, and knocking down USP44 decreases Foxp3 expression, disrupting the Treg gene expression pattern (inhibiting IL-2 expression) [78]. In addition, both USP44 and USP7 expression reduce the ubiquitination of Foxp3, and there is a synergistic effect between these two deubiquitinating enzymes (DUBs) [38]. When coexpressed, these proteins almost completely eliminate the polyubiquitination of Foxp3. Research indicates that USP44 directly interacts with the Hedgehog signalling pathway and can interact with the E3 ligase Itch, stabilizing it through deubiquitination. This leads to proteasome degradation of Gli1 and subsequent decreased activity of the Hedgehog pathway, ultimately inhibiting PD-L1 expression and the development of hepatocellular carcinoma [38]. However, no related reports exist in breast cancer. Therefore, in breast carcinoma, USP44 may also promote the development of breast carcinoma through its involvement in Hedgehog signalling and affect breast cancer immunity by inhibiting PD-L1 expression. This issue still requires further research for verification.

USP9X

USP9X is located on chromosome Xp11. 4 and is composed of several structural domains, including a ubiquitin-like (UBL) domain, a catalytic domain with a specific cysteine residue and histidine box motifs. The catalytic domain of USP9X contains a finger subdomain that includes zinc finger motifs and three ubiquitin binding sites, along with a β-erfhin insertion. This domain helps in processing and cleaving polyubiquitin chains linked via Lys11, Lys63, Lys48, and Lys6, enabling proteins to perform various cellular functions [79].

The T-cell receptor (TCR) signalling cascade comprises a diverse array of proteins and molecules crucial for transmitting TCR signals during antigen recognition. These include TCR complexes, CD3 complexes, ζ chains, key protein kinases such as Lck, ZAP-70, and MAP kinases, adaptors such as LAT (T-cell activating connexin) and SLP-76, and transcription factors [80]. Effective T-cell activation occurs only when these constituents function cohesively to prevent spontaneous activation. USP9X enhances TCR-dependent phosphorylation, catalytic viability, and binding to the LAT signalling complex, facilitating ZAP70 deubiquitination and initiating T-cell activation [81]. The survival of B cells relies on the B-cell receptor (BCR) and NF-κB, with PKCβ kinase exerting a positive regulatory influence on the BCR and NF-κB. Additionally, USP9X can modulate PKCβ kinase activity. As a deubiquitinating enzyme for Bcl10, USP9X controls the formation of CBM complexes elicited by activated TCRs. These CBM complexes, comprising CARMA1 (CARD11), Bcl10, and MALT1, represent a central signalling hub within the NF-κB activation pathway. Consequently, USP9X can significantly influence the NF-κB signalling pathway, thereby crucially affecting T lymphocyte activation. Knockdown of USP9X markedly diminishes CARMA1 phosphorylation levels, resulting in decreased CBM complex formation and reduced cell dependency on NF-κB for survival [82].

The Notch pathway is activated in TNBC [83]. Proinflammatory cytokines and tumour-associated macrophages are further secreted and recruited into the tumour microenvironment when this pathway is activated [84–86]. Knockdown of USP9X does not activate the Notch pathway, resulting in a decrease in the secretion of the proinflammatory cytokines C-C motif chemokine ligand 2 (CCL2) and interleukin-1β (IL-1β) [87]. CCL2 and IL-1β are predictive factors of poor prognosis in breast carcinoma patients and play a significant role in the recruitment of the immune environment. TAMs can promote tumour angiogenesis, improve the migration and invasion of breast cancer cells, and suppress the cytotoxicity of T lymphocytes (CTLs). Finally, they lead to the progression of cancer. After Notch deactivation, there can be a reduction in the production of proinflammatory cytokines, resulting in an immunogenic tumour phenotype. The immunosuppressive tumour phenotype ultimately leads to reduced tumour growth. Blocking USP9X using genetic or pharmacological methods can result in Notch inactivation, which positively regulates the immune response in this context. Additionally, USP9X promotes antigen receptor signalling processes in T and B lymphocytes and is essential for regulating immune memory to achieve long-lasting immune responses [87]. USP9X regulates the antigen-specific clonal expansion of CD4 + T cells and promotes their survival. Both of these processes are inseparable from the formation and development of immune memory [81](Table 1).

Table 1 Roles of USPs in the Immune Microenvironment of breast Cancer

Molecules	Target(s)	Findings	Influence
USP7	Foxp3; M2 macrophage	1.USP7 deubiquitination stabilizes Foxp3 and Tip60, thereby enhancing the immunosuppressive function of Treg cells to promote tumour growth [37]. 2.Exosomal circ-0100519 induces M2 macrophage polarization and promotes breast cancer progression through the USP7/NRF2 axis [25].	Immune escape
USP8	TGF-β/SMAD signalling; PD-L1; Foxo1	1. Inhibition of USP8 can antagonize TGF-β/SMAD signalling and reduce the stability of TβRII and the number of TβRII + crEVs to prevent exhaustion of CD8 + T cells and reinvigorate antitumour immunity [56]. 2.USP8 regulates the protein stability of PD-L1, affecting the immune escape of tumours [47]. 3.USP8 maintains the normal homeostasis of T cells by upregulating IL-7R release mediated by Foxo1 [58].	Immune escape
USP12	T cell; NF-κB signalling pathway; PD-L1	1.USP12 stabilizes BCL10 through deubiquitination and activates the NF-κB signalling pathway, thereby activating CD4 + T-cell responses [17]. 2.Downregulating USP12 can accelerate the ubiquitination and degradation of PPM1B, thereby promoting the activity of NF-κB in coordinating the TME [96]. 3.Silencing USP12 enhances the expression of PD-L1 in tumour cells [60].	immunosuppressive microenvironment
USP15	IFN signalling; TGF-β signalling pathway; T cell; Tregs; myeloid-derived suppressor cells; PD-L1	1. Several cellular substrates of USP15 directly participate in immune responses and IFN signalling transduction [63]. 2.USP15 can also regulate tumour immune-related pathways, such as the TGF-β signalling pathway [64]. 3.USP15 is a key regulatory factor in T-cell activation [6]. 4.The lack of USP15 leads to the overactivation of IFN-γ T cells, resulting in the upregulation of PD-L1 and CXCL12 expression, as well as the enhanced recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), further promoting the formation of an immunosuppressive microenvironment [67].	immune responses
USP21/22	Foxp3; PD-L1; Treg; T cell; MDSCs	1.USP21 regulates the stability of Foxp3 protein at the posttranslational modification level [39]. 2.The overexpression of USP21 also significantly increases the abundance of PD-L1, while its knockdown induces PD-L1 degradation [76]. 3.USP22 influences Treg function by promoting the level of Foxp3 [40]. 4.The loss of USP22 can lead to a significant reduction in MDSCs in the TME, promoting the infiltration of T cells and NK cells. Conversely, the expression of USP22 confers resistance of tumours to immunotherapy. Depletion of USP22 enhances T-cell-mediated cytotoxicity [72]. 5.USP22 interacts with SPI1 and enhances the stability of SPI1 through deubiquitination, thereby regulating the expression of PD-L1. It modulates the protein level of PD-L1 through the USP22-CSN5-PD-L1 axis [75].	Immune escape
USP44	Foxp3	1.Knocking down USP44 decreases the expression of Foxp3, thereby disrupting the Treg gene expression pattern [78].	Immunity homeostasis
USP9X	NF-κB signalling pathway; T lymphocyte; B lymphocytes	1.USP9X serves as a deubiquitinase for Bcl10 and functionally regulates the formation of the TCR-triggered CBM complex, thereby modulating the NF-κB signalling pathway in T cells [82]. 2.USP9X is a positive regulatory factor in antigen receptor signalling in T and B lymphocytes, and is essential for regulating immune memory and enabling long-lasting immune responses [81].	Immune escape

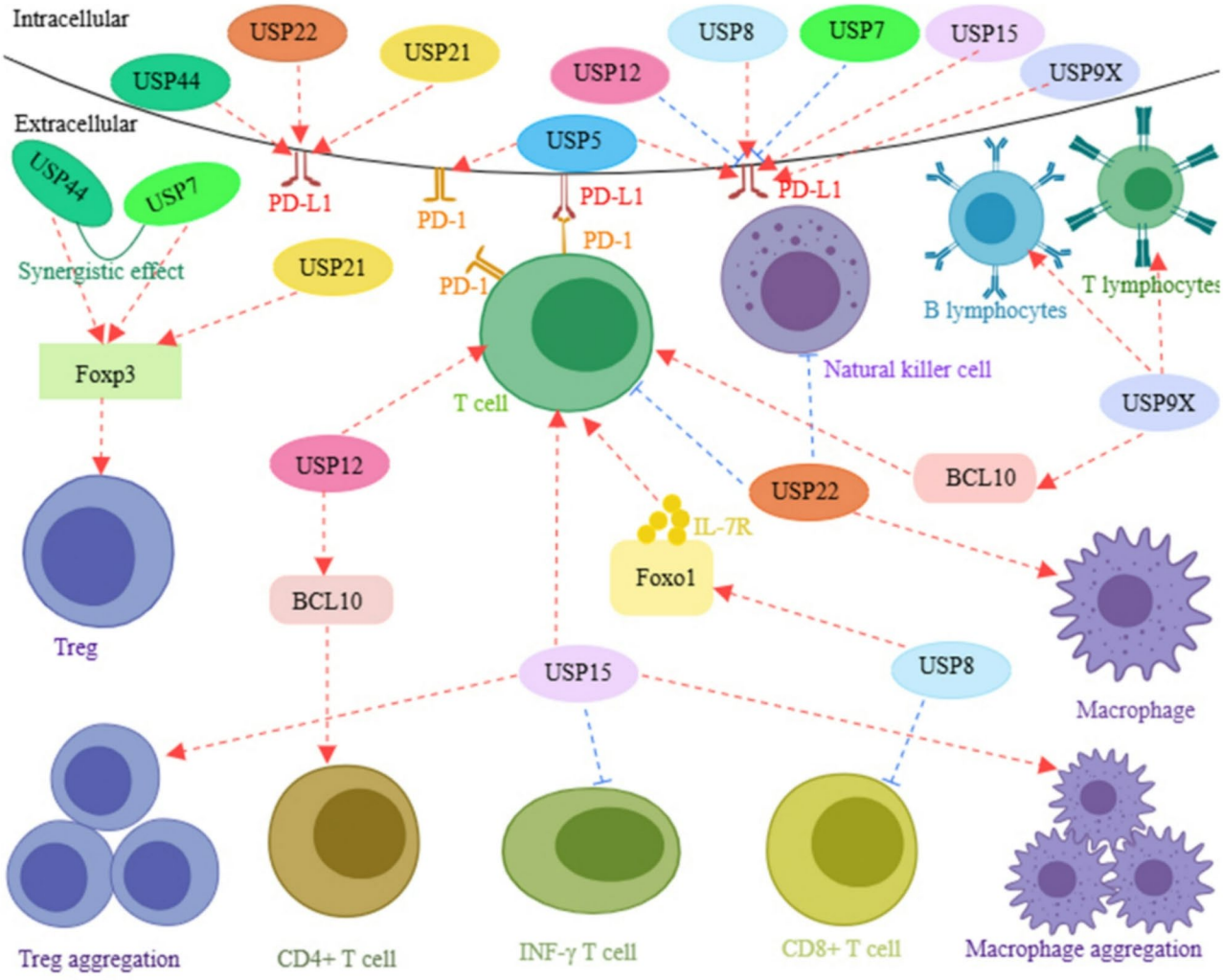

Fig. 3 Ubiquitin-specific proteases affect various cells in the tumour Microenvironment USP12, USP7, USP8, USP15, USP21, USP22, USP44 and USP9X promote PD-L1 expression, whereas USP5 promotes the expression of both PD-L1 and PD-1. USP7, USP44, and USP21 positively regulate Tregs, and USP15 promotes the recruitment of Tregs and macrophages and inhibits INF-γ T cells. In T cells, USP8, USP12, USP15, and USP9X play positive regulatory roles, with USP12 positively regulating CD4 + T cells and USP8 negatively regulating CD8 + T cells. USP22 promotes macrophages but inhibits natural killer cells and T cells. Additionally, USP9X positively regulates T lymphocytes and B lymphocytes

The application and prospects of immunotherapy in breast cancer

The current principal strategies for cancer immunotherapy include immune checkpoint inhibitors, tumor vaccines, and immune cell therapies. Research indicates that the attenuated poliovirus vaccine may represent a potential therapeutic approach for breast cancer [88], while modifications to the oncolytic virus genome, along with the insertion of requisite transgenes, offer promising avenues for the treatment of pancreatic cancer [89]. Among these, immune checkpoint inhibitors constitute a pivotal area of exploration in breast cancer immunotherapy. Nonetheless, owing to weak immunogenicity in breast cancer, monotherapy with immunotherapy is ineffective, thus emphasizing the necessity of employing combination therapy to enhance treatment outcomes. USPs regulate various aspects of immune function, including congenital immunity and inflammatory responses, and affect the signalling processes of immune cells. They are important immune influential factors. Several studies have indicated the involvement of specific USPs in the immune regulation of breast cancer, potentially impacting the level of PD-1/PD-L1, thereby leading to immune evasion. Consequently, the utilization of USP inhibitors presents an opportunity to increase the efficacy of immunotherapy. At present, a number of ubiquitin-specific protease inhibitors have been shown to be effective in the treatment of breast cancer and display synergistic effects in conjunction with immune checkpoint inhibitors. For example, inhibitors of USP1, such as trifluridine, rottlerin, and ML323, have demonstrated significant effects. Trifluridine impedes the growth and brain metastasis of

TNBC cancer tumours by inducing G0/G1 arrest and apoptosis [90]. Rottlerin prompts autophagy, culminating in the apoptosis of breast tumour stem cells, and might also have antiangiogenic effects on breast tumour cells [91, 92]. For breast cancer patients who already have metastases, the mechanism by which the USP7 inhibitor costoglulactone inhibits breast cancer involves targeting the regulation of the cell cycle, thereby inducing the occurrence of apoptosis in breast tumour cells [93], and dehydrolactones work synergistically with it [6]. Additionally, the USP14 inhibitor auranofin exhibits synergistic effects in the treatment of triple-negative breast cancer when combined with vitamin C or anti-PD-L1 antibodies. Furthermore, it holds potential for combination therapy with crizotinib in breast cancer treatment [94]. Additionally, the USP14 inhibitor auranofin has synergistic effects in treating triple-negative breast cancer when it is used in combination with vitamin C or with anti-PD-L1 antibodies. Furthermore, it has potential for combined utilization with crizotinib for breast cancer treatment [94]. USP14 inhibition sensitizes BRCA1-mutant and PARP inhibitor-resistant TNBC cells to poly(ADP-ribose) glycohydrolase (PARG) inhibitors [95]. USP8 inhibitors can upregulate the expression of PD-L1, triggering immune responses and antigen presentation. Therefore, their combination with immune checkpoint inhibitors can reduce the growth of tumour cells.

While this review highlights the significant role of USPs in breast cancer progression and immune modulation, several limitations warrant consideration. Firstly, the existing literature primarily focuses on a limited number of USPs, which may overlook the potential roles of lesser-studied USPs in breast cancer. Additionally, many of the studies discussed are preclinical, and therefore, the translation of these findings into clinical practice requires further validation through clinical trials.Moreover, our understanding of the precise mechanisms by which USPs influence the immune microenvironment remains incomplete. Future research should aim to elucidate the specific pathways involved in USP-mediated regulation of immune responses and tumor biology. Investigating the crosstalk between USPs and various immune cells within the tumor microenvironment could provide deeper insights into their roles in immune evasion and resistance to therapies.

Conclusion

This review highlights the significant role of USPs in the immune microenvironment and immune responses associated with breast cancer. As a focal point in the regulation of immune cell functions, USPs contribute to crucial processes such as antigen processing, T cell development, and the differentiation of immune cells, including myeloid-derived suppressor cells and regulatory T cells. Their influence extends to critical factors like PD-L1 expression, ultimately impacting the efficacy of immune checkpoint inhibitors. The differential expression of USPs is closely linked to immune evasion and treatment resistance, indicating their dual role as facilitators of tumor progression and obstacles to effective therapy. Further exploration of the regulation of USPs in the immune microenvironment of breast cancer is needed, which can offer a theoretical foundation for the clinical application of USP inhibitors.

Given the complexities of breast cancer treatment in the era of precision medicine, targeting USPs emerges as a promising strategy to enhance the effectiveness of immunotherapy. By combining USP inhibitors with traditional and novel therapeutic agents, it may be possible to improve patient outcomes and mitigate resistance mechanisms. Therefore, further clinical investigation into the modulation of USPs may pave the way for innovative treatment approaches that better address the challenges inherent in breast cancer therapy, offering hope for improved survival and quality of life for affected individuals.

Abbreviations

TILs	Tumour-infiltrating lymphocytes
USPs	Ubiquitin-specific proteases
PD-L1	Programmed cell death ligand-1
MDSCs	Myeloid-derived suppressor cells
TAMS	Tumour associated macrophages
Tregs	Regulatory T cells
PD-1	Programmed death 1
HLA-I	Human leukocyte antigen class I
Th1	Type 1 helper T cells
DCs	Dendritic cells
TME	Tumour microenvironment
VEGF	Vascular endothelial growth factor
BFGF	Basic fibroblast growth factor
MMP9	Matrix metalloproteinase 9
IL-12	Interleukin 12
Foxp3	Forehead Box Protein P3
TNF-α	Tumour necrosis factor
IL-1β	Interleukin-1 beta
tTregs	: Thymus-derived Tregs
pTregs	Peripheral Tregs
iTregs	Iduced Tregs
E1	Ubiquitin-activating enzyme
E2	Ubiquitin-conjugating enzyme
E3	Ubiquitin ligase
TCR	T-cell receptor
ESCRT	Endosomal sorting complex required for transport
TRAF6	TNF receptor-associated factor 6
TET	Ten-eleven translocation
α-KG	α-ketoglutarate
TAK1	TGF-β-activated kinase 1
SAGA	Spt-Ada-Gcn5-acetyltransferase
ATXN7/Sgf73	SAGA-associated factor 73
ENY2/Sus1	Sugar isomerase 1
DUBm	SAGA complex
ORF	Open reading frame
DUBs	Deubiquitinating enzymes
UBL	Ubiquitin-like domain
TCR	The T-cell receptor
LAT	T-cell activating connexin
BCR	B-cell receptor

CCL2	C-C motif chemokine ligand 2
IL-1β	Interleukin-1β
CTLs	Cytotoxicity of T lymphocytes
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
PARG	Poly(ADP-ribose) glycohydrolase

Supplementary Information

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Supplementary Material 1

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Author contributions
H.Yang and D.Wu designed the research study; T.Sun, Z.Sun, H.Wang, D.Liu, T.Qin, and M.Zhou performed the research; H.Yang and T.Qin has been involved in drafting the manuscript and all authors have been involved in revising it critically for important intellectual content.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All the authors have agreed on the contents of the manuscript.

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The authors declare no competing interests.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and Mortality Worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
2. Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, et al. Current and future burden of breast cancer: global statistics for 2020 and 2040. Breast. 2022;66:15–23.
3. Li YW, Dai LJ, Wu XR, Zhao S, Xu YZ, Jin X, et al. Molecular characterization and classification of HER2-Positive breast Cancer inform tailored therapeutic strategies. Cancer Res. 2024;84:3669–83.
4. Agostinetto E, Curigliano G, Piccart M. Emerging treatments in HER2-positive advanced breast cancer: keep raising the bar. Cell Rep Med. 2024;5:101575.
5. Ye F, Dewanjee S, Li Y, Jha NK, Chen ZS, Kumar A, et al. Advancements in clinical aspects of targeted therapy and immunotherapy in breast cancer. Mol Cancer. 2023;22:105.
6. Gao H, Yin J, Ji C, Yu X, Xue J, Guan X, et al. Targeting ubiquitin specific proteases (USPs) in cancer immunotherapy: from basic research to preclinical application. J Exp Clin Cancer Res. 2023;42:225.
7. Zhao Z, Lin Z, Guo X, Al-Danakh A, He H, Qin H et al. Ubiquitin-Specific Protease 43 Impacts Pancreatic Ductal Adenocarcinoma Prognosis by Altering Its Proliferation and Infiltration of Surrounding Immune Cells. J Immunol Res. 2023; 2023: 4311388.
8. Gao H, Xi Z, Dai J, Xue J, Guan X, Zhao L, et al. Drug resistance mechanisms and treatment strategies mediated by ubiquitin-specific proteases (USPs) in cancers: new directions and therapeutic options. Mol Cancer. 2024;23:88.
9. Harris MA, Savas P, Virassamy B, O'Malley MMR, Kay J, Mueller SN, et al. Towards targeting the breast cancer immune microenvironment. Nat Rev Cancer. 2024;24:554–77.
10. Kundu M, Butti R, Panda VK, Malhotra D, Das S, Mitra T, et al. Modulation of the tumor microenvironment and mechanism of immunotherapy-based drug resistance in breast cancer. Mol Cancer. 2024;23:92.
11. Baxevanis CN, Fortis SP, Perez SA. The balance between breast cancer and the immune system: challenges for prognosis and clinical benefit from immunotherapies. Semin Cancer Biol. 2021;72:76–89.
12. Wang X, Deng X, Hu J, Zheng W, Ye D, Zhou X, et al. K48-linked deubiquitination of VGLL4 by USP15 enhances the efficacy of tumor immunotherapy in triple-negative breast cancer. Cancer Lett. 2024;588:216764.
13. Zhu X, Wang P, Zhan X, Zhang Y, Sheng J, He S, et al. USP1-regulated reciprocal differentiation of Th17 cells and Treg cells by deubiquitinating and stabilizing TAZ. Cell Mol Immunol. 2023;20:252–63.
14. Xiao X, Shi J, He C, Bu X, Sun Y, Gao M, et al. ERK and USP5 govern PD-1 homeostasis via deubiquitination to modulate tumor immunotherapy. Nat Commun. 2023;14:2859.
15. Chen SW, Zhu SQ, Pei X, Qiu BQ, Xiong D, Long X, et al. Cancer cell-derived exosomal circUSP7 induces CD8(+) T cell dysfunction and anti-PD1 resistance by regulating the miR-934/SHP2 axis in NSCLC. Mol Cancer. 2021;20:144.
16. Leon-Ferre RA, Jonas SF, Salgado R, Loi S, de Jong V, Carter JM, et al. Tumor-infiltrating lymphocytes in Triple-negative breast Cancer. JAMA. 2024;331:1135–44.
17. Fu Y, Wang P, Zhao J, Tan Y, Sheng J, He S, et al. USP12 promotes CD4(+) T cell responses through deubiquitinating and stabilizing BCL10. Cell Death Differ. 2021;28:2857–70.
18. Fang W, Zhou T, Shi H, Yao M, Zhang D, Qian H, et al. Progranulin induces immune escape in breast cancer via up-regulating PD-L1 expression on tumor-associated macrophages (TAMs) and promoting CD8(+) T cell exclusion. J Exp Clin Cancer Res. 2021;40:4.
19. Lasser SA, Ozbay Kurt FG, Arkhypov I, Utikal J, Umansky V. Myeloid-derived suppressor cells in cancer and cancer therapy. Nat Rev Clin Oncol. 2024;21:147–64.
20. Lu J, Luo Y, Rao D, Wang T, Lei Z, Chen X, et al. Myeloid-derived suppressor cells in cancer: therapeutic targets to overcome tumor immune evasion. Exp Hematol Oncol. 2024;13:39.
21. Ruocco MR, Gisonna A, Acampora V, D'Agostino A, Carrese B, Santoro J et al. Guardians and mediators of Metastasis: exploring T lymphocytes, myeloid-derived suppressor cells, and Tumor-Associated macrophages in the breast Cancer Microenvironment. Int J Mol Sci. 2024;25(11):6224.
22. Rajkumari S, Singh J, Agrawal U, Agrawal S. Myeloid-derived suppressor cells in cancer: current knowledge and future perspectives. Int Immunopharmacol. 2024;142:112949.
23. Xia J, Zhang L, Peng X, Tu J, Li S, He X, et al. IL1R2 blockade alleviates immunosuppression and potentiates Anti-PD-1 efficacy in Triple-negative breast Cancer. Cancer Res. 2024;84:2282–96.
24. Dai Q, Wu W, Amei A, Yan X, Lu L, Wang Z. Regulation and characterization of tumor-infiltrating immune cells in breast cancer. Int Immunopharmacol. 2021;90:107167.
25. Zhuang M, Zhang X, Ji J, Zhang H, Shen L, Zhu Y, et al. Exosomal circ-0100519 promotes breast cancer progression via inducing M2 macrophage polarisation by USP7/NRF2 axis. Clin Transl Med. 2024;14:e1763.
26. Qian J, Li J, Ma H, Ji W. Exosomal circ-ADRM1 promotes lung adenocarcinoma progression and induces macrophage M2 polarization through regulating MMP14 mRNA and protein. Anticancer Drugs. 2023;34:333–43.
27. Qiu X, Zhao T, Luo R, Qiu R, Li Z. Tumor-Associated macrophages: Key players in Triple-negative breast Cancer. Front Oncol. 2022;12:772615.
28. Guo R, Wang P. The complex role of regulatory cells in breast cancer: implication for immunopathogenesis and immunotherapy. Breast Cancer. 2024.
29. Wang Y, Johnson KCC, Gatti-Mays ME, Li Z. Emerging strategies in targeting tumor-resident myeloid cells for cancer immunotherapy. J Hematol Oncol. 2022;15:118.
30. Lv Y, Wang G, Gao R, Zhu G, Liu R. Preliminary study on the significance of pathological characteristics analysis of breast cancer and detection of peripheral blood myeloid-derived suppressor cells in the evaluation of biological characteristics. Biotechnol Genet Eng Rev. 2024;40:4599–610.

31. Huang X, Cao J, Zu X. Tumor-associated macrophages: an important player in breast cancer progression. Thorac Cancer. 2022;13:269–76.
32. Wan Y, Mu X, Zhao J, Li L, Xu W, Zhang M. Myeloid–derived suppressor cell accumulation induces Treg expansion and modulates lung malignancy progression. Biomed Rep. 2024;20:68.
33. Ichiyama K, Long J, Kobayashi Y, Horita Y, Kinoshita T, Nakamura Y, et al. Transcription factor Ikzf1 associates with Foxp3 to repress gene expression in Treg cells and limit autoimmunity and anti-tumor immunity. Immunity. 2024;57:2043–60. e2010.
34. Varveri A, Papadopoulou M, Papadovasilakis Z, Compeer EB, Legaki AI, Delis A, et al. Immunological synapse formation between T regulatory cells and cancer-associated fibroblasts promotes tumour development. Nat Commun. 2024;15:4988.
35. Malla RR, Vasudevaraju P, Vempati RK, Rakshmitha M, Merchant N, Nagaraju GP. Regulatory T cells: their role in triple-negative breast cancer progression and metastasis. Cancer. 2022;128:1171–83.
36. Sarkar T, Dhar S, Chakraborty D, Pati S, Bose S, Panda AK, et al. FOXP3/HAT1 Axis Controls Treg Infiltration in the Tumor Microenvironment by inducing CCR4 expression in breast Cancer. Front Immunol. 2022;13:740588.
37. Wang F, Wang L, Wu J, Sokirniy I, Nguyen P, Bregnard T, et al. Active site-targeted covalent irreversible inhibitors of USP7 impair the functions of Foxp3 + T-regulatory cells by promoting ubiquitination of Tip60. PLoS ONE. 2017;12:e0189744.
38. Chen S, Zhou B, Huang W, Li Q, Yu Y, Kuang X, et al. The deubiquitinating enzyme USP44 suppresses hepatocellular carcinoma progression by inhibiting hedgehog signaling and PDL1 expression. Cell Death Dis. 2023;14:830.
39. Li Y, Lu Y, Wang S, Han Z, Zhu F, Ni Y, et al. USP21 prevents the generation of T-helper-1-like Treg cells. Nat Commun. 2016;7:13559.
40. Cortez JT, Montauti E, Shifrut E, Gatchalian J, Zhang Y, Shaked O, et al. CRISPR screen in regulatory T cells reveals modulators of Foxp3. Nature. 2020;582:416–20.
41. Li J, Wang S, Wang N, Zheng Y, Yang B, Wang X, et al. Aiduqing formula inhibits breast cancer metastasis by suppressing TAM/CXCL1-induced Treg differentiation and infiltration. Cell Commun Signal. 2021;19:89.
42. Schildberg FA, Klein SR, Freeman GJ, Sharpe AH. Coinhibitory pathways in the B7-CD28 ligand-receptor family. Immunity. 2016;44:955–72.
43. Chen X, Feng L, Huang Y, Wu Y, Xie N. Mechanisms and strategies to overcome PD-1/PD-L1 Blockade Resistance in Triple-negative breast Cancer. Cancers (Basel). 2022;15(1):104.
44. Wei Y, Xiao X, Lao XM, Zheng L, Kuang DM. Immune landscape and therapeutic strategies: new insights into PD-L1 in tumors. Cell Mol Life Sci. 2021;78:867–87.
45. Mandai M, Hamanishi J, Abiko K, Matsumura N, Baba T, Konishi I. Dual faces of IFNγ in Cancer Progression: a role of PD-L1 induction in the determination of Pro- and Antitumor Immunity. Clin Cancer Res. 2016;22:2329–34.
46. Wei Y, Zhao Q, Gao Z, Lao XM, Lin WM, Chen DP, et al. The local immune landscape determines tumor PD-L1 heterogeneity and sensitivity to therapy. J Clin Invest. 2019;129:3347–60.
47. Xiong W, Gao X, Zhang T, Jiang B, Hu MM, Bu X, et al. USP8 inhibition reshapes an inflamed tumor microenvironment that potentiates the immunotherapy. Nat Commun. 2022;13:1700.
48. Singer M, Elsayed AM, Husseiny MI. Regulatory T-cells: the face-off of the Immune Balance. Front Biosci (Landmark Ed). 2024;29:377.
49. Liu J, Wang X, Deng Y, Yu X, Wang H, Li Z. Research Progress on the Role of Regulatory T Cell in Tumor Microenvironment in the treatment of breast Cancer. Front Oncol. 2021;11:766248.
50. Dvir K, Giordano S, Leone JP. Immunotherapy in breast Cancer. Int J Mol Sci. 2024;25(14):7517.
51. Cruz L, Soares P, Correia M. Ubiquitin-specific proteases: players in Cancer Cellular processes. Pharmaceuticals (Basel). 2021;14(9):848.
52. Saha G, Roy S, Basu M, Ghosh MK. USP7 - a crucial regulator of cancer hallmarks. Biochim Biophys Acta Rev Cancer. 2023;1878:188903.
53. van Loosdregt J, Fleskens V, Fu J, Brenkman AB, Bekker CP, Pals CE, et al. Stabilization of the transcription factor Foxp3 by the deubiquitinase USP7 increases Treg-cell-suppressive capacity. Immunity. 2013;39:259–71.
54. D'Angelo D, De Martino M, Arra C, Fusco A. Emerging role of USP8, HMGA, and non-coding RNAs in Pituitary Tumorigenesis. Cancers (Basel). 2019;11(9):1302.
55. Huang Y, Xia L, Tan X, Zhang J, Zeng W, Tan B, et al. Molecular mechanism of lncRNA SNHG12 in immune escape of non-small cell lung cancer through the HuR/PD-L1/USP8 axis. Cell Mol Biol Lett. 2022;27:43.
56. Xie F, Zhou X, Li H, Su P, Liu S, Li R, et al. USP8 promotes cancer progression and extracellular vesicle-mediated CD8 + T cell exhaustion by deubiquitinating the TGF-β receptor TβRII. Embo j. 2022;41:e108791.
57. Yang H, Zhang X, Lao M, Sun K, He L, Xu J, et al. Targeting ubiquitin-specific protease 8 sensitizes anti-programmed death-ligand 1 immunotherapy of pancreatic cancer. Cell Death Differ. 2023;30:560–75.
58. Dufner A, Kisser A, Niendorf S, Basters A, Reissig S, Schönle A, et al. The ubiquitin-specific protease USP8 is critical for the development and homeostasis of T cells. Nat Immunol. 2015;16:950–60.
59. Niu K, Shi Y, Lv Q, Wang Y, Chen J, Zhang W, et al. Spotlights on ubiquitin-specific protease 12 (USP12) in diseases: from multifaceted roles to pathophysiological mechanisms. J Transl Med. 2023;21:665.
60. Zhan X, He Q, Sheng J, Jiang X, Lin L, Huang Y, et al. USP12 positively regulates M-MDSC function to inhibit antitumour immunity through deubiquitinating and stabilizing p65. Immunology. 2022;167:544–57.
61. Yang Z, Xu G, Wang B, Liu Y, Zhang L, Jing T, et al. USP12 downregulation orchestrates a protumourigenic microenvironment and enhances lung tumour resistance to PD-1 blockade. Nat Commun. 2021;12:4852.
62. Das T, Song EJ, Kim EE. The multifaceted roles of USP15 in Signal Transduction. Int J Mol Sci. 2021;22(9):4728.
63. Chen LL, Smith MD, Lv L, Nakagawa T, Li Z, Sun SC et al. USP15 suppresses tumor immunity via deubiquitylation and inactivation of TET2. Sci Adv. 2020;6(38):eabc9730.
64. Georges A, Gros P, Fodil N. USP15: a review of its implication in immune and inflammatory processes and tumor progression. Genes Immun. 2021;22:12–23.
65. Zhou Q, Cheng C, Wei Y, Yang J, Zhou W, Song Q, et al. USP15 potentiates NF-κB activation by differentially stabilizing tables 2 and table 3. Febs j. 2020;287:3165–83.
66. Zou Q, Jin J, Hu H, Li HS, Romano S, Xiao Y, et al. USP15 stabilizes MDM2 to mediate cancer-cell survival and inhibit antitumor T cell responses. Nat Immunol. 2014;15:562–70.
67. Zou Q, Jin J, Xiao Y, Zhou X, Hu H, Cheng X, et al. T Cell Intrinsic USP15 Deficiency promotes excessive IFN-γ production and an immunosuppressive Tumor Microenvironment in MCA-Induced Fibrosarcoma. Cell Rep. 2015;13:2470–9.
68. An T, Lu Y, Yan X, Hou J. Insights into the properties, Biological functions, and regulation of USP21. Front Pharmacol. 2022;13:944089.
69. Feng T, Ling S, Xu C, Ying L, Su D, Xu X. Ubiquitin-specific peptidase 22 in cancer. Cancer Lett. 2021;514:30–7.
70. Gregory S, Xu Y, Xie P, Fan J, Gao B, Mani N, et al. The ubiquitin-specific peptidase 22 is a deubiquitinase of CD73 in breast cancer cells. Am J Cancer Res. 2022;12:5564–75.
71. Zhang Y, Wang Y, Gao B, Sun Y, Cao L, Genardi SM et al. USP22 controls iNKT immunity through MED1 suppression of histone H2A monoubiquitination. J Exp Med. 2020;217(5):e20182218.
72. Guo J, Zhao J, Sun L, Yang C. Role of ubiquitin specific proteases in the immune microenvironment of prostate cancer: a new direction. Front Oncol. 2022;12:955718.
73. Li Q, Zhang L, You W, Xu J, Dai J, Hua D, et al. PRDM1/BLIMP1 induces cancer immune evasion by modulating the USP22-SPI1-PD-L1 axis in hepatocellular carcinoma cells. Nat Commun. 2022;13:7677.
74. Huang X, Zhang Q, Lou Y, Wang J, Zhao X, Wang L, et al. USP22 Deubiquitinates CD274 to suppress anticancer immunity. Cancer Immunol Res. 2019;7:1580–90.
75. Guo J, Zhao J, Fu W, Xu Q, Huang D. Immune Evasion and Drug Resistance mediated by USP22 in Cancer: novel targets and mechanisms. Front Immunol. 2022;13:918314.
76. Yang S, Yan H, Wu Y, Shan B, Zhou D, Liu X, et al. Deubiquitination and stabilization of PD-L1 by USP21. Am J Transl Res. 2021;13:12763–74.
77. Lou Y, Ye M, Xu C, Tao F. Insight into the physiological and pathological roles of USP44, a potential tumor target (review). Oncol Lett. 2022;24:455.
78. Yang J, Wei P, Barbi J, Huang Q, Yang E, Bai Y, et al. The deubiquitinase USP44 promotes Treg function during inflammation by preventing FOXP3 degradation. EMBO Rep. 2020;21:e50308.
79. Meng Y, Hong C, Yang S, Qin Z, Yang L, Huang Y. Roles of USP9X in cellular functions and tumorigenesis (review). Oncol Lett. 2023;26:506.
80. Acuto O, Di Bartolo V, Michel F. Tailoring T-cell receptor signals by proximal negative feedback mechanisms. Nat Rev Immunol. 2008;8:699–712.
81. Naik E, Dixit VM. Usp9X is required for lymphocyte activation and homeostasis through its control of ZAP70 ubiquitination and PKCβ kinase activity. J Immunol. 2016;196:3438–51.

82. Park Y, Jin HS, Liu YC. Regulation of T cell function by the ubiquitin-specific protease USP9X via modulating the Carma1-Bcl10-Malt1 complex. Proc Natl Acad Sci U S A. 2013;110:9433–8.
83. Stylianou S, Clarke RB, Brennan K. Aberrant activation of notch signaling in human breast cancer. Cancer Res. 2006;66:1517–25.
84. Jin L, Yuan RQ, Fuchs A, Yao Y, Joseph A, Schwall R, et al. Expression of interleukin-1beta in human breast carcinoma. Cancer. 1997;80:421–34.
85. Kolb R, Liu GH, Janowski AM, Sutterwala FS, Zhang W. Inflammasomes in cancer: a double-edged sword. Protein Cell. 2014;5:12–20.
86. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. Nature. 2011;475:222–5.
87. Naik E, Webster JD, DeVoss J, Liu J, Suriben R, Dixit VM. Regulation of proximal T cell receptor signaling and tolerance induction by deubiquitinase Usp9X. J Exp Med. 2014;211:1947–55.
88. Vazeh H, Behboudi E, Hashemzadeh-Omran A, Moradi A. Live-attenuated poliovirus-induced extrinsic apoptosis through caspase 8 within breast cancer cell lines expressing CD155. Breast Cancer. 2022;29:899–907.
89. Hamidi-Sofiani V, Rakhshi R, Moradi N, Zeynali P, Nakhaie M, Behboudi E. Oncolytic viruses and pancreatic cancer. Cancer Treat Res Commun. 2022;31:100563.
90. Feng Z, Xia Y, Gao T, Xu F, Lei Q, Peng C, et al. The antipsychotic agent trifluoperazine hydrochloride suppresses triple-negative breast cancer tumor growth and brain metastasis by inducing G0/G1 arrest and apoptosis. Cell Death Dis. 2018;9:1006.
91. Kumar D, Shankar S, Srivastava RK. Rottlerin-induced autophagy leads to the apoptosis in breast cancer stem cells: molecular mechanisms. Mol Cancer. 2013;12:171.
92. Yin X, Zhang Y, Su J, Hou Y, Wang L, Ye X, et al. Rottlerin exerts its anti-tumor activity through inhibition of Skp2 in breast cancer cells. Oncotarget. 2016;7:66512–24.
93. Roy A, Manikkam R. Cytotoxic impact of Costunolide isolated from Costus speciosus on breast Cancer via Differential Regulation of Cell Cycle-An In-vitro and In-silico Approach. Phytother Res. 2015;29:1532–9.
94. Pal A, Donato NJ. Ubiquitin-specific proteases as therapeutic targets for the treatment of breast cancer. Breast Cancer Res. 2014;16:461.
95. Li P, Zhu X, Qu H, Han Z, Yao X, Wei Y, et al. Synergistic effect of ubiquitin-specific protease 14 and poly(ADP-Ribose) glycohydrolase co-inhibition in BRCA1-Mutant, poly(ADP-Ribose) polymerase inhibitor-resistant triple-negative breast Cancer cells. Onco Targets Ther. 2024;17:741–53.
96. Jahan AS, Lestra M, Swee LK, Fan Y, Lamers MM, Tafesse FG, et al. Usp12 stabilizes the T-cell receptor complex at the cell surface during signaling. Proc Natl Acad Sci U S A. 2016;113:E705–714.

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