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REVIEW

Emerging potential of ubiquitin-specific proteases and ubiquitin-specific proteases inhibitors in breast cancer treatment

Mei-Ling Huang, Guang-Tai Shen, Nan-Lin Li

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Abstract

Breast cancer is the most frequently diagnosed cancer in women, accounting for 30% of new diagnosing female cancers. Emerging evidence suggests that ubiquitin and ubiquitination played a role in a number of breast cancer etiology and progression processes. As the primary deubiquitinases in the family, ubiquitin-specific peptidases (USPs) are thought to represent potential therapeutic targets. The role of ubiquitin and ubiquitination in breast cancer, as well as the classification and involvement of USPs are discussed in this review, such as USP1, USP4, USP7, USP9X, USP14, USP18, USP20, USP22, USP25, USP37, and USP39. The reported USPs inhibitors investigated in breast cancer were also summarized, along with the signaling pathways involved in the investigation and its study phase. Despite no USP inhibitor has yet been approved for clinical use, the biological efficacy indicated their potential in breast cancer treatment. With the improvements in phenotypic discovery, we will know more about USPs and USPs inhibitors, developing more potent and selective clinical candidates for breast cancer.

Key Words: Ubiquitin-specific proteases; USPs inhibitors; Breast cancer; Review

Core Tip: Ubiquitin-specific proteases (USPs) are emerging as potential therapeutic targets in many diseases. In breast cancer, several USPs were overexpressed. In this study, we summarize the involvement of USPs in breast cancer and the development of USP inhibitors, providing more reference to discover potent and selective clinical candidates.

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women, accounting for 30% of newly diagnosed cancers in females, an increase of 18% over lung cancer[1]. Emerging evidence suggests that dysregulation of the ubiquitin-proteasome system may play a critical role in the development and progression of breast cancer by affecting protein homeostasis, protein-protein interactions, and signal transduction[2]. Ubiquitination can regulate pathways involving tumor promotion and suppression in cancer[3]. Deubiquitinating enzymes (DUBs), mediating the ubiquitin removal and processing, might be functionally important but are less well understood. So far, about 100 human DUBs have been identified, over 90% of them are cysteine-proteases, containing conserved cysteine (C), histidine (H) in catalytic sites. DUBs are divided into the following super families: ovarian tumor protease, ubiquitin specific protease (USP), Machado-Josephin domain superfamily, ubiquitin C-terminal hydrolase (UCH), and zinc-containing metalloproteases. Similar to kinases, the ubiquitination system's components are frequently dysregulated, which results in a number of illnesses, including tumorigenesis[4].

Ubiquitin-proteasome system, consisting of ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), ubiquitin-ligase (E3), and the 26S proteasome, plays significant roles in various cellular proteins for breast cancer genesis[5]. Many well-studied proteins in the clinical breast cancer, like Skp2 (S-phase kinase-associated protein 2), BRCA1, BARD1, Efp *etc*., are major participants in the ubiquitination pathway[6]. Through PDCD4 ubiquitination, Skp2, the first F-box protein discovered, was deregulated to increase radiation tolerance and breast cancer carcinogenesis[7]. The BRCA1/BARD1 RING complex, functioning as an ubiquitin (Ub) ligase, abolished in familial breast cancer with deleterious missense mutations of BRCA1[8]. Ueki *et al*[9] proved that overexpression of the ubiquitin-conjugating enzyme E2T could result in the autoubiquitination and proteosomal destruction of BRCA1. Besides, ubiquitin-proteasome pathway may be crucial in the treatment of breast cancer patients who take anthracyclines[10]. One of the causes of advanced breast cancer's resistance to hormone therapy may be the estrogen-responsive E3 ubiquitin ligase Efp, which selectively targets 14-3-3 sigma for destruction[11]. Consequently, ubiquitin and ubiquitination played a role in a number of elements of the pathophysiology and development of breast cancer. In this report, we provide greater context for finding potent and targeted clinical candidates by summarizing the discovery of USP inhibitors and the role of USPs in breast cancer in this study (Figure 1).

UBIQUITIN-SPECIFIC PROTEASE FAMILY

USPs, with more than 50 members, constitute the largest DUBs family. USPs can remove ubiquitin from specific protein substrates, allowing protein salvage and protein localization or activation regulation. All USPs feature highly conserved USP domains made up of three subdomains that resemble the right hand's palm, thumb, and fingers[12]. The finger domain is in charge of interactions with distal ubiquitin, and the catalytic site is situated between the palm and thumb domains[13]. Despite their relative structural diversity with additional domains and terminal extensions, most USPs shared the common feature of a typical conformational change. Upon ubiquitin binding, USPs drive the transition from an inactive form to a catalytically active state[14]. The first shown X-ray structure of USP protein was the catalytic core of HAUSP/USP7[15]. The crystal structure of the 45-kDa catalytic domain of USP14 was reported in 2005[16]. In 2018, Ward *et al*[17] reported that the structure of the deubiquitinase USP15 reveals a misaligned catalytic triad and an open ubiquitin-binding channel (Figure 2).

USPS AND BREAST CANCER

USPs belonging to cysteine proteases, are aberrantly expressed in tumors or their microenvironment, making them promising candidates as target for drug development[18]. The majority of USPs, including USP1, USP4, USP7, USP9X, USP14, USP18, USP20, USP22, USP25, USP37 and USP3, were overexpressed in breast cancer (Table 1)[19].

USP1

USP1, one of the best-characterized DUBs, is crucial in the control of DNA repair procedures. In breast cancer, USP1 inhibition was reported to suppress breast cancer metastasis *via* KPNA2[20]. Besides, USP1

Table 1 Ubiquitin-specific proteases studied in breast cancer

USPs	Expression	Potential role in breast cancer	Signal pathway
USP1	Upregulated	Tumor promoter	KPNA2, ERα signaling, Hippo signaling pathway, TGF-β signaling[20-23]
USP4	Upregulated	Tumor suppressor	PDCD4, circBMPR2, PAK5-DNPEP pathway, Relaxin/TGF-β1/Smad2/MMP-9 signaling, TGF-β signaling[24-28]
USP7	Upregulated	Tumor promoter	PHF8,DNA repair, Aurora-A kinase, ECT2[29-34]
USP9X	Upregulated	Tumor promoter, Tumor suppressor	CEP131, Hippo Pathway, Notch signaling, Cyclin D1,Wnt signaling, TRAIL, YAP1[35,37,38,40,41,45,46]
USP11	Upregulated	Tumor promoter	TGFβ signaling, DNA damage, XIAP[47-49]
USP14	Upregulated	Tumor promoter	CyclinB1, Wnt/β-catenin and PI3K/AKT pathways, cell cycle[53,54]
USP15	Upregulated	Tumor promoter	DNA repair, ERα signaling[65,66]
USP18	Upregulated	Tumor promoter	AKT/Skp2 pathway[68]
USP20	Upregulated	Tumor promoter	SNAI2[69]
USP22	Upregulated	Tumor promoter	c-Myc, Hh pathway[57,58]
USP28	Upregulated	Tumor suppressor	HIF-independent pathway, LSD1[71,72]
USP32	Upregulated	Tumor promoter	Unknown[73]
USP33	Upregulated	Tumor suppressor	Slit-Robo signaling[74]
USP37	Upregulated	Tumor promoter	Stemness, epithelial-mesenchymal transition[60]
USP39	Upregulated	Tumor promoter	G0/G1-phase arrest, CHEK2[62,63]

USPs: Ubiquitin-specific peptidases; KPNA2: Karyopherin subunit α-2; ER: Estrogen receptor; TGF-β: Transforming growth factor-β; PDCD4: Programmed cell death 4 protein; circBMPR2: Bone morphogenetic protein 2; PAK5: P21-activated kinase; DNPEP:Aspartyl aminopeptidase; MMP-9: Matrix metallopeptidase 9;Smad2: Small mothers against decapentaplegic 2; PHF8: Plant homeodomain finger protein 8; DNA: Deoxyribonucleic acid; ECT2: Epithelial cell transforming 2; CEP131: Centrosomal protein 131; TRAIL: TNF-related apoptosis-inducing ligand; YAP1: Yes-associated protein 1; XIAP: X-linked inhibitor of apoptosis protein; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; Skp2: S-phase kinase-associatedprotein 2; SNAI2: Snail family transcriptional repressor 2; Hh: Hedgehog; HIF: Hypoxia inducible factor-1; LSD1: Human lysine specific demethylases l; CHEK2: checkpoint kinase 2.

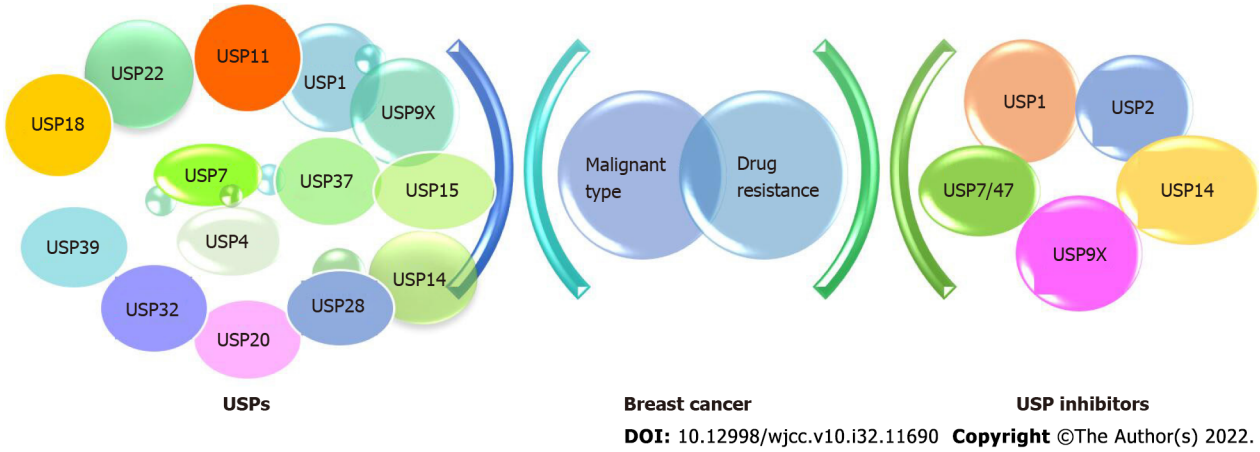

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Figure 1 Graphaic figure of the review. USPs: Ubiquitin-specific peptidases.

was proved as a novel TAZ (WWTR1) regulator to increase breast cancer cell proliferation and migration[21]. USP1's non-genomic mechanism, which stabilizes the ER protein, can also hasten the development of breast cancer[22]. For triple negative breast cancer, a unique function of the USP1 was lighted in promoting TGF-β-induced EMT and migration *via* stabilization of TAK1[23].

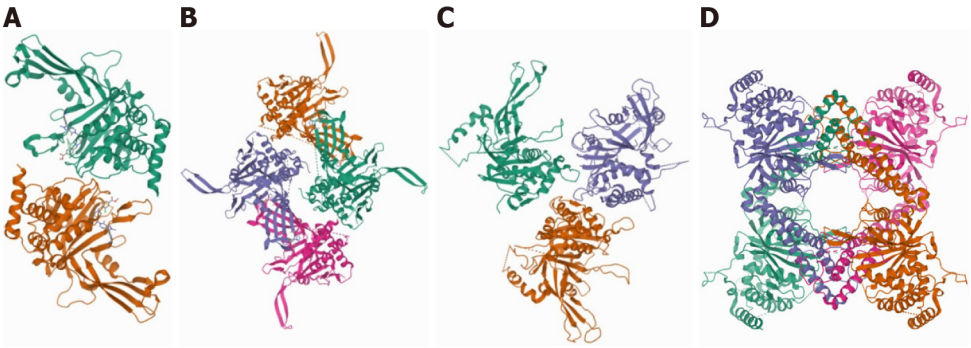

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Figure 2 Crystal structure of ubiquitin-specific peptidases. A: Ubiquitin-specific peptidases (USP) 7 in complex with a novel inhibitor; B: Crystal structure of the catalytic domain of human USP9X; C: Structure of USP14; D: Structure of human USP25.

USP4

Ubiquitin-specific protease 4 (USP4) is located in chromosome 3 (3p21,3) and identified as a tumor suppressor in breast cancer[24]. It was discovered that circBMPR2 acts as a miR-553 sponge and relieves USP4 repression to stop the spread of tamoxifen resistance of breast cancer[25]. Additionally discovered as a downstream target of the PAK5-DNPEP pathway, USP4 controls the growth and spread of breast cancer[26]. Besides, USP4 was an important determinant for the crosstalk between the TGF-β and AKT signalling pathways[27]. The signal from relaxin/TGF-1/Smad2/MMP-9 may be the mechanism *via* which USP4 encourages breast cancer invasion[28].

USP7

USP7, also known as Herpesvirus associated protease, is a 128 kDa cysteine protease and member of the USP DUB family. The grade of breast cancer's histology was strongly linked with USP7 overexpression [29]. USP7 strongly enhanced apoptotic gene expression and reduced metastasis of breast cancer cell lines[30]. USP7 can deubiquitinate and stabilize ECT2, ultimately maintaining oncogenic protein MDM2 levels in breast carcinogenesis[31]. Furthermore, ERα status is essential to the function of USP7 in breast carcinogenesis, ERα overexpression can rescue the USP7 silencing-induced cell cycle arrest and apoptosis[32]. Breast cancer was discovered to have a relationship between USP7 and the taxanes response, suggesting that the USP7 protein may be a potential predictor of outcome[33]. Stability of Aurora-A kinase affected by USP7 may be the possible mechanism in regulating mitosis progression and taxane sensitivity[34].

USP9X

Numerous studies have shown that USP9x has a pro-carcinogenic influence on the development of breast cancer[35,36]. Hippo pathway[37], Notch signaling[38,39], cyclin-dependent pathway[40], and Wnt signaling were a few of the potential signaling pathways[41]. Additionally, USP9X contributed to the medication resistance in breast cancer. Tamoxifen, but not the ER downregulator fulvestrant, was able to stop proliferation due to the loss of activity in the deubiquitinase USP9X[42]. In breast cancer cells lacking the estrogen receptor, USP9X inhibition may improve cisplatin sensitivity[43]. Olaparib and methyl methanesulfonate are PARP inhibitors that are much more sensitive when USP9X is knocked down[44]. By interacting with β-catenin through deubiquitination in breast cancer cells, USP9x can be used as a therapeutic target for TRAIL-resistant breast cancers[45]. USP9X-YAP1 axis maybe an important regulatory mechanism to elevates cell sensitivity to chemotherapy[46].

USP11

USP11 takes involvement in a variety of cellular metabolic activities. In human breast cancer, USP11-mediated alteration of TGF-downstream signaling may increase EMT and metastasis[47]. USP11 also participates in DNA damage repair, involving in the BRCA2 pathway independently of BRCA2 deubiquitination[48]. Regulation of XIAP turnover reveals a role for USP11 inpromotion of breast tumorigenesis[49]. In addition, USP11 was discovered to be a novel ER transcriptional regulator in breast cancer and was linked to a poor prognosis in ER+ patients[50]. USP11 was also linked to outcome prediction in breast cancer patients after neoadjuvant therapy[51].

USP14

By eliminating ubiquitin chains from its substrates, USP14 prevents the breakdown of ubiquitinated proteins, but it can also speed up the process by enhancing proteasome activation. USP14 has a role in the spread of breast cancer by encouraging proliferation and metastasis while blocking apoptosis[52]. AR deubiquitination is critical for breast cancer growth and USP14 inhibition is a possible strategy to

treat AR-positive breast cancer[53]. USP14 can regulate the cell cycle of breast cancer cells by regulating CyclinB1 ubiquitination[54]. Besides, USP14 inhibition could enhance the sensitivity of breast cancer to enzalutamide by AR-related signaling pathways, such as PI3K/AKT and Wnt/β-catenin pathways[55].

USP22

The expression level of USP22 protein, an independent prognostic factor for overall survival (OS) and disease-free survival of breast cancer, was significantly higher than that in breast fibroadenoma and normal breast tissues[56]. In murine and breast cancer cells, USP22 favorably controlled c-Myc stability and tumorigenic activity[57]. Additionally, USP22's deubiquitination activity was necessary for it to maintain ER stability, which improved ER action and conferred endocrine resistance in breast cancer [58].

USP37

Ubiquitin specific peptidase 37 (USP37), composed of 979 amino acids harboring three ubiquitin-interacting motifs between the Cys box and His box of the primary sequence, is a member of ubiquitin-specific processing proteases family localized mainly in the cytoplasm. USP37 was an independent poor prognostic biomarker for OS, recurrence-free survival and metastasis-free survival, dividing the luminal and triple negative breast cancer into subgroups with different prognosis[59]. In addition, USP37 can regulate the stemness, cell invasion, EMT and sensitivity to cisplatin in breast cancer cells[60]. USP37 knockdown could reverse the resistance of breast cancer cells to Adriamycin. USP37 down-regulation might be a potential strategy against ADR resistance in breast cancer treatment[61].

USP39

Ubiquitinspecific protease 39 (USP39) encodes a 65 kDa SR-associated protein, exhibits aberrant an expression and has oncogenic functions in several types of cancer. The identification of USP39 as a potential molecular target for breast cancer gene therapy was generated following the study of Wang and colleagues[62]. USP39 c.*208G>C was strongly associated with triple-negative breast tumors, regulating cancer-relevant tumor suppressor[63]. USP39 downregulation obviously reduced the proliferation and colony-forming ability of triple-negative breast cancer cells[64].

Others

Limited exploration about USP15, USP18, USP20, USP28, USP32 and USP51 in breast cancer were published. As novel protector for preventing ERα degradation, USP15 is critical driver for breast cancer progression[65]. In addition, cancer-associated USP15 mutations could decrease USP15-BARD1 interaction and increases PARP inhibitor sensitivity in cancer cells[66]. USP18 mRNA levels in human breast tumor tissues were substantially greater in ER+-than in ER−breast cancer tissues. USP18 mRNA levels in ER+-tumor tissues were substantially greater than in their equivalent tumor-adjacent tissues [67]. USP18 may accelerate breast cancer growth by upregulating EGFR and activating the AKT/Skp2 pathway[68]. Higher USP20 expression was linked to a worse prognosis in patients with ER- breast cancer, suggesting that USP20 may facilitate the spread of breast cancer[69]. USP28 participated in various cancers including breast cancer, intestinal cancers, gliomas, non-small cell lung cancer, and bladder cancer[70]. Overexpression of USP28 correlated with a better survival in patients with invasive ductal breast carcinoma[71]. USP28 stabilized LSD1 and conferred stem-cell-like traits to breast cancer cells[72]. USP32 was overexpressed in 50% of breast cancer cell lines and 22% of primary breast tumors compared to mammary epithelial cells[73]. USP33 was also found overexpressed and inhibit breast metastasis[74]. USP51 was found to be a bona fide target of CDK4/6, and could be a viable therapeutic target for advanced human cancers[75]. There have been some new research on the relationship between USPs and breast cancer development in recent years, but more proof is still required.

DEVELOPMENT USPS INHIBITORS IN BREAST CANCER TREATMENT

Since USPs and molecular signaling pathways are tightly connected, several efforts have been made to develop USPs inhibitors. Prior to 2014, the discovery of USP inhibitors reported mainly relied on high-throughput screening. Recently, based on the co-crystal structures of USP-inhibitor complexes, structure-guided drug design was conducted. In past ten years, USPs inhibitors have started to gradually emerge. More than 60 USPs inhibitors were reported and two of them (b-AP15 and VLX1570) was under clinical trial for multiple myeloma treatment[14]. For breast cancer, several USPs inhibitors were studied (Table 2), but none have been authorized for clinical use (Figure 3).

USP1 inhibitor

Pimozide has been widely studied as a potential anticancer treatment in various cancers, including breast, lung, central nervous system tumours, prostate, melanoma, osteosarcoma, neuroblastoma, ovarian, colorectal, myeloproliferative neoplasms, pancreatic, and hepatocellular carcinoma[76]. Back to

Table 2 Reported ubiquitin-specific peptidases inhibitors in breast cancer study

Target		Breast cancer subtype	Experiment	Pathways
USP1	Pimozide	ER negative BC, TNBC	*In vitro*; *In vivo*	Cell cycle, AKT signaling pathway, EMT, MMP-9, vimentin, STAT3[76,78,79]
	Trifluoperazin	TNBC	*In vitro*; *In vivo*	G0/G1 arrest, cyclinD1/CDK4, cyclinE/CDK2[80]
	Rottlerin	ER positive BC, TNBC, CSCs	*In vitro*	NFκB, cyclin D-1, p38 MAPK, AMPK, proteasome inhibition, Skp2[81-84]
	ML323	BC	*In vitro*; *In vivo*	KPNA2[20]
USP2	6-TG	BRCA2-defective PARP inhibitor-resistant BC, BRCA1-mutant BC, TNBC	*In vitro*; *In vivo*	DNA repair, PI3K-AKT, apoptosis pathway, lncRNA-miRNA-mRNA ceRNA network, DNMT1[85,87,88,90]
	ML364	ER-positive BC	*In vitro*	Endocytic degradation[91]
USP7	Costunolide	metastatic TNBC, BC	*In vitro*	NF-κB signaling, cell cycle regulation, c-Myc/p53, AKT/14-3-3 pathway, p38MAPK pathways[92-95]
USP7/47	P5091	BC	*In vitro*	EMT[96]
USP14	b-AP15	ER positive BC, TNBC	*In vitro*; *In vivo*	Autophagy, ERα signaling[98,99]
	IU1	AR-positive BC	*In vitro*; *In vivo*	Wnt/β-catenin, PI3K/AKT pathways [55]
	Auranofin	ER positive BC, TNBC	*In vitro*; *In vivo*	PTGR1 expression, ERK1/2-MYC, p38 MAPK signaling pathway, mitochondrial apoptosis[100-102]
USP9x	WP1130	ER-negative BC	*In vitro*	Mcl-1[43]

USPs: Ubiquitin-specific peptidases; ER: Estrogen receptor; BC: Breast cancer; TNBC: Triple-negative breast cancer; AKT: Protein kinase B; EMT: Epithelial mesenchymal transition; MMP-9: Matrix metallopeptidase 9; STAT3: Signal transducerand activator of transcription 3; CDK: Cyclin-Dependent Kinase; NFκB: Nuclear factor kappa-B; MAPK: Mitogen-activated protein kinase; AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; Skp2: S-phase kinase-associatedprotein 2; KPNA2: Karyopherinα2; CSCs: Cancer stem cells; BRCA: Breast cancer 1; PARP: Poly (ADP-ribose) polymerase; DNA: Deoxyribonucleic acid; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; lncRNA: Long non-coding RNA; miRNA: MicroRNA; ceRNA: Competing endogenous RNA; DNMT1: DNA (cytosine-5-)-methyltransferase 1; AR: Androgen receptor; MAPK: Mitogen-activated protein kinase; PTGR1: Prostaglandin reductase 1; ERK1/2: Extracellular regulated protein kinases 2; Mcl-1: Myeloid cell leukemia-1.

1992, pimozide was regarded as potential noncytotoxic alternatives to tamoxifen for the treatment of tamoxifen-resistant human breast cancer[77]. Antitumor activity of pimozide against breast cancer development was demonstrated by suppressing angiogenesis and by paracrine stimulation[78]. In triple-negative breast cancer, Pimozide could dramatically lessen invasion and migration *via* phosphorylating STAT3[79].

Trifluoperazin, Rottlerin and ML323 were all USP1 inhibitors. By causing G0/G1 arrest and apoptosis, trifluoperazine hydrochloride was discovered to inhibit the growth of triple-negative breast cancer tumors and brain metastasis[80]. Rottlerin could exhibit antiangiogenic effects in breast cancer cells[81,82]. The fact that rottlerin induces autophagy, which results in apoptosis for breast cancer stem cells, suggests that rottlerin may be a safe therapy option for breast cancer[83,84]. Limited study was reported about ML323 in breast cancer, KPNA2 maybe the targets of ML323 in suppressesing breast cancer metastasis[20].

USP2 inhibitor

Only two USP2 inhibitors were reported in breast cancer application. 6-thioguanine (6-TG) was reported to selectively kill BRCA2-defective tumors and overcomes PARP inhibitor resistance[85]. BRCA1-deficient breast cancer cell lines are distinct sensitivities to 6-TG[86]. The function of 6-TG in triple-negative breast cancer was involved with lncRNA[87,88].

Differentially expressed genes and competitive endogenous (ce)RNA molecules may have contributed to the mechanism by which 6-TG inhibits the development of MCF-7 cells[89,90]. Another USP2 inhibitor, ML364, may make breast cancer cells that are HER2-positive more susceptible to HSP90 inhibition[91].

USP7, USP7/47 inhibitor

USP 7 inhibitor costunolide suppress breast cancer growth and metastases and may be promising anticancer drugs, especially for metastatic breast cancer[92]. By targeting cell cycle regulation, costu-

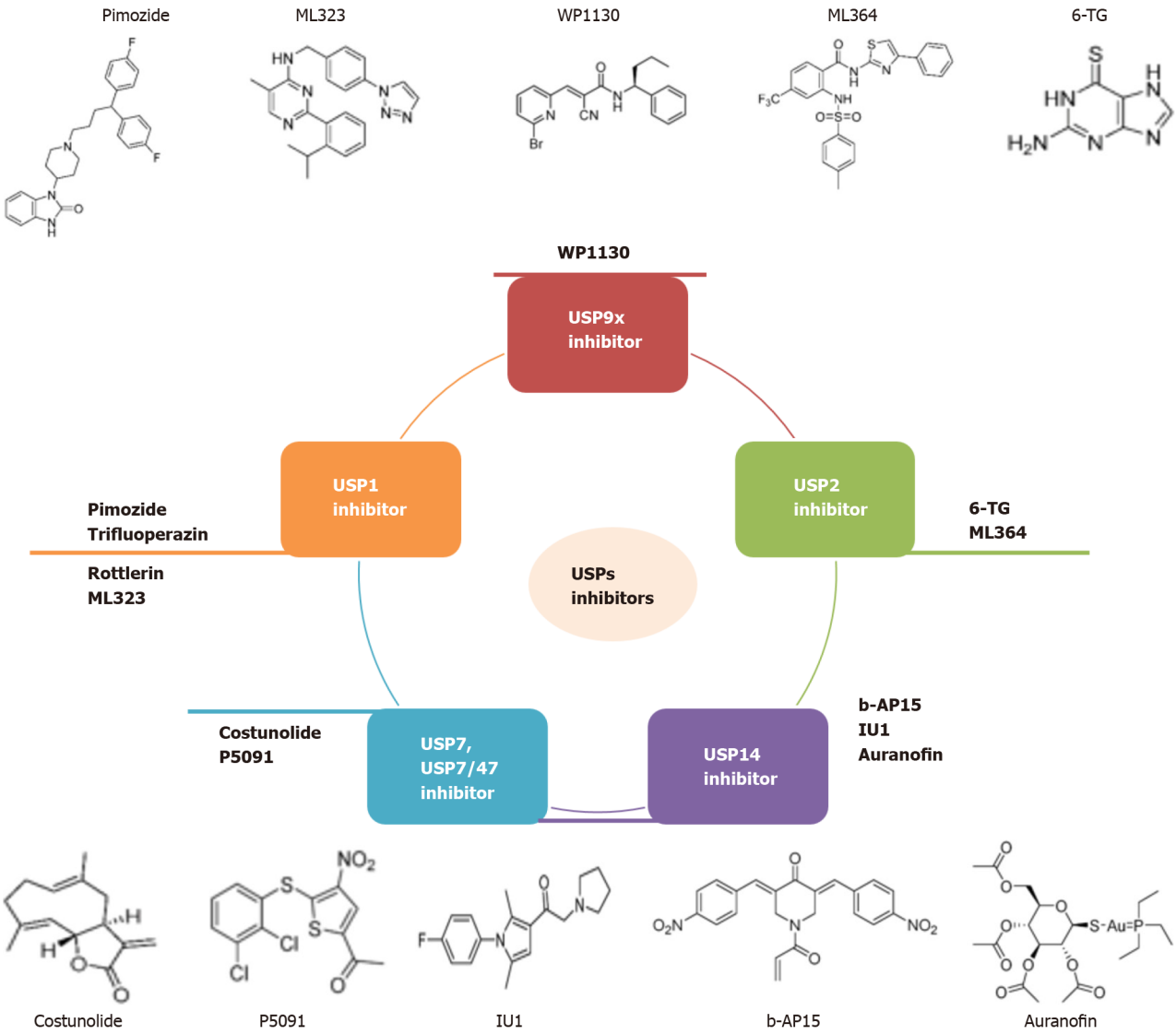

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Figure 3 Ubiquitin-specific peptidases inhibitors. USPs: Ubiquitin-specific peptidases; 6-TG: 6-thioguanine.

nolide effectively induced breast cancer cell apoptosis[93]. Combination treatment of costunolide and dehydrocostuslactone could inhibit breast cancer by inducing cell cycle arrest and apoptosis[94]. The control of Bax, Bcl-2, p53, Caspase-3 protein production as well as the activation of the p38MAPK and nuclear factor-B (NF-B) pathways were essential components of the apoptotic mechanism[95].

The USP7/47 inhibitor P5091 was able to reverse morphological alterations in MCF-10A cells and lower the expression of EMT markers[96]. Blockage of deubiquitination by P5091 could reduce cell proliferation, colony formation, migration, and sphere dissemination for breast cancer cell lines[30].

USP14 inhibitor

Proteasome-associated deubiquitinases (USP14 and UCHL5) inhibitors b-AP15 can inhibit tumor progression of MCF-7 breast cancer cell line[97]. In 2015, the effect of b-AP15 and RA-9 on triple negative breast cancer cell lines was proved[98]. Moreover, b-AP15 and PtPT may have the potential for the treatment of estrogen receptor-positive breast cancer[99].

Auranofin, a USP14 inhibitor, demonstrated synergistic breast cancer inhibition. The combination of Auranofin and Vitamin C was efficient against triple-negative breast cancer[100]. Cooperation was found between auranofin and anti-PD-L1 antibody for treatment of triple-negative breast cancer[101]. A unique therapeutic approach for breast cancer may be used to take advantage of the synergistic effects of auranofin and trametinib[102]. In addition, IU1, another USP14 inhibitor, had the capacity to improve enzalutamide's ability to suppress cell proliferation and induce apoptosis in breast cancer cell lines both *in vitro* and *in vivo*[55].

USP9x inhibitors

USP9x inhibitor was rarely reported. It was discovered that WP1130 increased the cytotoxicity of cisplatin in ER-negative breast cancer cells. In the meantime, simultaneous therapy with WP1130 may improve cisplatin sensitivity in estrogen receptor-negative breast cancer cells in a USP9x-dependent manner[43].

CONCLUSION

USPs are a highly specialized class of DUBs with emerging potential in breast cancer. USPs involved into many important signaling pathways, including ERα signaling, Hippo signaling pathway, TGF-β signaling, PI3K/AKT pathways, Notch signaling, *etc.* USPs have garnered more attention as possible targets, and USPs inhibitors have begun to progressively appear. Although no USP inhibitor has been authorized for clinical use to far, biological efficacy suggested they may be useful in the treatment of breast cancer. We will learn more about USPs and USPs inhibitors as phenotypic discovery advances, leading to the identification of more effective and targeted therapeutic candidates for breast cancer.

FOOTNOTES

Author contributions: Shen GT and Li NL designed the research study and guide the writing; Huang ML performed the research, analyzed the data and wrote the manuscript; Shen GT guide the revision of the manuscript; all authors have read and approve the final manuscript. Huang ML and Shen GT contributed equally to this work.

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