



WW domain binding protein 2 (WBP2) as an oncogene in breast cancer: mechanisms and therapeutic prospects—a narrative review

Yan Liu^{1#}, Enping He^{2#}, Yanling Zhang³, Yitong Liu¹, Yingshuang Wang¹, Siyu Chen¹, Xinyu Wu¹, Youqing Zeng¹, Ping Leng¹

¹Chongqing Key Laboratory of Sichuan-Chongqing Co-construction for Diagnosis and Treatment of Infectious Diseases Integrated Traditional Chinese and Western Medicine, College of Medical Technology, Chengdu University of Traditional Chinese Medicine, Chengdu, China; ²The Second Affiliated Hospital of Chengdu Medical College (China National Nuclear Corporation 416 Hospital), Chengdu, China; ³Department of Clinical Laboratory, Ya'an People's Hospital, Ya'an, China

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[#]These authors contributed equally to this work and should be considered as co-first authors.

Correspondence to: Youqing Zeng; Ping Leng. Chongqing Key Laboratory of Sichuan-Chongqing Co-construction for Diagnosis and Treatment of Infectious Diseases Integrated Traditional Chinese and Western Medicine, College of Medical Technology, Chengdu University of Traditional Chinese Medicine, 1166 Liutai Avenue, Wenjiang District, Chengdu 611137, China. Email: zengyouqin@163.com; lengping@cductcm.edu.cn.

Background and Objective: WW domain binding protein 2 (*WBP2*), considered an emerging breast cancer gene, functions as a binding partner for WW domain proteins. The *WBP2* gene is involved in mediating the malignant development and clinical drug resistance of breast cancer, but its potential mechanism remains unclear. Therefore, it is necessary to elucidate the mechanism of *WBP2* in breast cancer, which will help to provide new methods for clinical diagnosis and treatment of breast cancer.

Methods: The PubMed database was searched using the terms “WW Domain Binding Protein 2” or “WBP2”, “breast cancer” or “breast neoplasms” or “human cancer” from January 1997 through August 2022. Through the screening and evaluation of titles and abstracts, about 120 English articles were included in this study.

Key Content and Findings: By describing the multiple regulatory functions of *WBP2* at the transcriptional, post-transcriptional, and post-translational levels, and summarizing how *WBP2* as a key node crosstalks multiple signaling pathways, we reveal the ability of *WBP2* to promote breast cancer malignant progression. In different subtypes of breast cancer, the mechanism of *WBP2*-mediated drug resistance is related to estrogen receptor and epidermal growth factor receptor (EGFR) 2 status, and hormones may be an essential factor in *WBP2*-mediated drug resistance. In addition, we discuss the application prospects of *WBP2* in targeted therapy and immunotherapy and propose therapeutic strategies to overcome drug resistance in breast cancer by jointly targeting *WBP2* and its related molecules. This provides a theoretical basis for the innovation of breast cancer targeted drugs.

Conclusions: *WBP2* is a promising target for breast cancer therapy. Nuclear *WBP2*, as the main functional form of *WBP2* after its activation, is a meaningful indicator for the diagnosis and prediction of breast cancer progression.

Keywords: WW domain binding protein 2 (*WBP2*); breast cancer; signaling pathway; drug resistance; combination therapy

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Introduction

Female breast cancer overtook lung cancer to become the most prevalent cancer worldwide in 2020 (1). Breast cancer is a highly heterogeneous malignancy originating from the epithelial tissue of the breast, which is a major cause of death in women (2). Early and locally advanced breast cancer can be almost cured by surgical resection combined with chemo-radiotherapy, endocrine therapy, and immunotherapy. However, breast cancer's heterogeneity and drug resistance notably limit the outcome and prognosis of patients, thus leading to the recurrence and metastasis of breast cancer. Patients with advanced metastatic breast cancer can only improve their quality of life with treatment and do not have the opportunity for a complete cure. Compared with the above treatment methods, the advantages of targeted therapy techniques with molecular specificity can be reflected. Targeted therapy has become a hot direction of tumor treatment because of its characteristics of strong pertinence, ready acceptance by patients, and small response. Therefore, it is of great significance to explore new oncogenes and important molecular markers in the molecular biology of breast cancer for the development of effective targeted inhibitors.

The WW domain binding protein 2 (*WBP2*) gene is a new breast cancer oncogene discovered in recent years. In 1995, *WBP2* was pinpointed as a homologous ligand for the Yes-associated protein (YAP) protein in the Hippo pathway (3). In the last 2 decades of research, it has been found to play an important role in promoting breast cancer progression. Protein tyrosine phosphorylation of *WBP2* is its major functional switch. Due to the regulation of multiple factors and signal channels, the RNA and protein levels of *WBP2* are differentially expressed. In this study, we explore the function of *WBP2* by parsing the regulation of *WBP2* at the transcriptional, post-transcriptional, and post-translational levels. Phosphorylated *WBP2* is a transcriptional coactivator that binds to WW domain-containing proteins, such as YAP (3), estrogen receptor (ER) (4), and progesterone receptor (PR) (5), through 3 C-terminal PPxY (PY) active regions, and activates the latter transcriptional activity to contribute to cancer development. Proteins that do not contain the WW domain can also interact with *WBP2*.

The binding position and mechanism of *WBP2* have been summarized in this paper to help clarify the functional mechanism of *WBP2*. Moreover, we found that 3 tyrosine activation pathways of *WBP2* in breast cancer are closely related to hormone receptor (HR) status. Therefore, we

consider that drug resistance in different subtypes of breast cancer is also specific, which may provide new ideas for the treatment and prevention of drug-resistant breast cancer, especially hormonally-mediated breast cancer. In addition, this paper discovered the application prospect of *WBP2* in immunotherapy and explored a new way of breast cancer treatment. Finally, we proposed the potential sites of action and combination therapy strategies of *WBP2* inhibitors, aiming to provide a reference direction for the development of clinically targeted drugs. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/ggs-22-716/rc>).

Methods

We searched for literature in the PubMed database. The search and screening processes are shown in *Table 1*.

WBP2 structure and functions

Structure of *WBP2* protein

The *WBP2* gene, which encodes the *WBP2* protein, is located at 17q25. Chromosome 17 is a strongly rearranged chromosome commonly seen in human cancers (6). The *WBP2* protein was first detached from the mouse embryo library (3). *WBP2* is composed of 261 amino acids with a molecular weight of 26–28 kD (*Figure 1*). *WBP2* contains an N-terminal pleckstrin homologous glucosyltransferase (PH-GRAM) domain and a C-terminal proline-rich (PR) domain. The 2 phosphorylation sites (192 and 231) in the PR domain indicate that it can be activated by tyrosine kinase and is inextricably linked to the *WBP2* function. In addition, the 3 PY motifs in the PR domain have been shown to have the function of participating in protein-protein interaction by binding to molecules containing the WW domain, which are called PY1, PY2, and PY3, respectively. The WW domain consists of 38–40 semi-conserved amino acids and was discovered in YAP (7). *WBP2* binds more strongly to the WW-PY region than *WBP1*, the other YAP ligand (8,9).

Functions of *WBP2*

Protein interactions mainly depend on the PY motif at the C-terminal domain of *WBP2* for binding to proteins containing the WW domain (10). *WBP2* plays a protein-protein interaction through 1 or more PY motifs. For

Table 1 The search strategies

Items	Specification
Date of search	August 1, 2022
Databases and other sources searched	PubMed
Search formula used	((WW Domain Binding Protein 2) OR (WBP2)) AND ((breast cancer) OR (breast neoplasms) OR (human cancer))
Timeframe	From January 1997 to August 2022
Inclusion and exclusion criteria	Retrospective study, preclinical studies, case report and studies not written in English were excluded
Selection process	Two co-first authors conducted initial screening by title and abstract. The included articles were read in full text. Eventually, all the authors participated in the discussion and received the same opinion

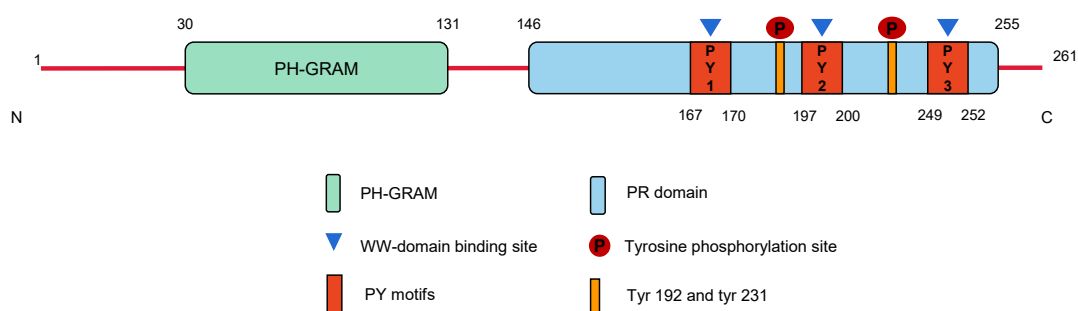


Figure 1 Structure of the WBP2 protein. The WBP2 protein contains a total of 261 amino acids and is mainly composed of a PH-GRAM at the N-terminus and a PR domain at the C-terminus. The PR domain comprises 3 PY motifs, PY1, PY2, and PY3, and 2 tyrosine phosphorylation sites, Tyr192 and Tyr231. The PY motifs are the main sites where WBP2 binds to WW domain-containing proteins and contribute to the protein interplay effect of WBP2. Tyr192 and Tyr231 are crucial sites for tyrosine phosphorylation of WBP2 and are closely related to the coactivation function of WBP2. N, N-terminus; C, C-terminus; P, tyrosine phosphorylation sites; PH-GRAM, pleckstrin homologous glucosyltransferase; PR, proline-rich; PY, PPxY; Tyr192, tyrosine 19; WBP2, WW domain binding protein 2.

example, the PY2 and PY3 motifs are vital for the WW domain binding interactions of transcriptional coactivator with PDZ-binding motif (TAZ) (11) and YAP (9), respectively. In contrast, the binding of WWC3 is linked to all 3 PY motifs of WBP2 (12). We can mutate different PY motif sites to initially distinguish the relative specificity and binding affinity of different binding substrates.

Coactivation functions belong to a special type of protein interactions, including transcriptional coactivation functions and non-transcriptional coactivation functions. For instance, WBP2 binds to transcription factors like YAP (9), TAZ (11), and β -catenin (13) to perform transcriptional co-activation functions. Further, WBP2 performs non-transcriptional co-activation with other proteins containing the WW domain, such as E6-associated

protein (5), WW and C2 domain-containing protein-3 (WWC3) (12), and α -enolase (ENO1) (14). The co-activation activity of WBP2 is unregulated by the absolute regulation of tyrosine phosphorylation at Tyrosine192 (Tyr192) and Tyr231 (10), suggesting that other parts of WBP2 are also crucial for its function.

Recently it has also been reported in the literature that WBP2 can interact with proteins lacking the WW domain, such as large tumor suppressor kinase 2 (LATS2) (15), and paired box 8 (Pax8) (16). Besides, the binding of neural precursor cells which expressed developmentally down-regulated 4 with the PR domain of WBP2 indicated that the regulation of protein stability was probably an alternative mode of transcriptional regulation by WBP2 (17). These pieces of evidence indicate that protein interactions of

WBP2 are not only restricted to PY-WW.

WBP2-associated cancers and diseases

Generally, WBP2 is highly expressed in most tumors, especially in breast cancer cells, which demonstrates the broad oncogenic potential of WBP2 in multiple organs. We summarize the biological functions and mechanisms mediated by WBP2 in all tumors in *Table 2*. WBP2 exerts oncogenic functions in these tumors and is associated with a poor clinical prognosis. Compared with ER or human epidermal growth factor receptor 2 (HER2) positive breast cancer, WBP2 has the highest expression and the worst prognosis in triple-negative breast cancer (TNBC).

Besides human cancers, WBP2 also plays important roles in other diseases. In the nervous system, the absence of *WBP2* can cause hearing impairment (26). WBP2 is also associated with neurological diseases like Huntington's disease and Alzheimer's disease (27,28). In the endocrine system, WBP2 can be involved in insulin signaling and lipid metabolism (29,30) and may also be involved in thyroid differentiation in conjunction with Pax8 (16). More than that, WBP2 can also be promoted to degradation by itchy E3 ubiquitin-protein ligase (ITCH) to attenuate the proliferation of CD4⁺ T cells and hence participate in the inflammatory response (31). In addition, WBP2 can activate oocytes, and takes the same position as WW binding protein 2 N-terminal like (WBP2NL) in mouse sperm (32). This finding provides strong evidence for WBP2's involvement in the development of the reproductive system. Recently, it was revealed that WBP2 was embroiled in apoptosis in monkey kidney cells, suggesting its potential role in the urinary system (33).

Transcriptional regulation of WBP2

Transcriptional regulation by transcription factor upstream transcription factor 1 (USF-1)

USF-1 is the only transcription factor identified so far that regulates WBP2. It contains an USF-specific region (USR) with the T153 residue, which is a functional region of USF-1 involved in transcriptional activation. The T153 residue activates the phosphorylation of USF-1. Phosphorylated USF-1 is further bound to E-box within the core of the *WBP2* promoter, thereby increasing *WBP2* transcription in breast cancer (30). Although another study demonstrated that USF-1 is a tumor suppressor (34), we believe that USF-1

remains a hazard factor for WBP2-positive breast cancer.

Besides, we believe that USF-1 and WBP2 may act as causative factors in insulin dysregulation-associated cancers because the insulin and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB/Akt) pathways control USF-1 phosphorylation (30). Heightened insulin is correlated with the occurrence and development of several cancers, like pancreatic cancer (35), endometrial cancer (36), and breast cancer (37). In this case, blocking USF-1 and *WBP2* loci may be a therapy for cancers associated with impaired insulin metabolism.

Post-transcriptional regulation by NcRNAs

MicroRNAs (miRNAs)

MiRNAs, as a member of non-coding RNAs (ncRNAs), bind to messenger RNA (mRNA) 3' untranslated regions (3' UTRs) to adjust gene expression by either translational inhibition or mRNA degradation. For example, miR-23a (38), miR-206 (18), and miR-613 (19) in breast cancer, and miR-485-5p (25) in hepatocellular carcinoma (HCC) all downregulate WBP2 expression by targeting the 3' UTRs. There is also a reverse regulatory mechanism for the biogenesis process of miRNAs by WBP2. As demonstrated by Tabatabaieian *et al.*, DiGeorge Critical Region 8 (DGCR8) is an essential component of the microprocessor complex, of which the oncogenic properties are inhibited by WBP2, leading to the disruption of downstream mature miRNA formation (21). The mechanism of this process is still unclear. We speculated that WBP2 may regulate the function of DGCR8 through physical binding effects or indirectly by participating in signaling pathways. The biological formation process of miRNAs and the bidirectional regulation of miRNAs and WBP2 are summarized in *Figure 2*.

Circular RNAs (circRNAs)

CircRNAs are a class of single-chain closed-loop ncRNAs formed by covalent bonds between the head and the tail. They are expected to be good biomarkers for early diagnosis and prognostic monitoring of cancer (39). CircRNAs that reside in the nucleus can regulate the transcription of their parental genes (40). Most of the circRNAs are spliced and transported into the cytoplasm, acting as sponges for miRNAs and inhibiting their negative regulation of target genes. Some circRNAs are also further transported as vesicles to the extracellular compartment or degraded by ribonuclease (39). CircPRKCI was upregulated in both

Table 2 The tumors related to WBP2

Tumor	Expression of WBP2	Interacting proteins/molecules	Correlation with WBP2	Clinical relevance	Signaling pathway	Biological function	Year	Refs
Breast cancer	Upregulated	ER α	Positive	–	ER	Inhibiting apoptosis Promoting doxorubicin resistance	2018	(6)
		ER α /c-Src/c-Yes	Positive	–	Wnt	Promoting growth, migration, invasion and tumorigenic	2011	(10)
		TAZ	Positive	–	Hippo	Promoting growth	2011	(11)
		ITCH	Negative	Poor prognosis, advanced pTNM stage, larger tumor sizes	Wnt	Promoting growth and invasion	2016	(13)
		miR-206	Negative	Poor prognosis	ER	Promoting proliferation and cell cycle Inhibiting apoptosis and tamoxifen sensitivity	2017	(18)
		miR-613	Negative	–	EGFR/PI3K/Akt	Promoting growth, proliferation and cell cycle Inhibiting apoptosis	2018	(19)
		HER2	Positive	Poor prognosis	EGFR	Promoting growth, proliferation and trastuzumab sensitivity Inhibiting cell cycle	2019	(20)
		DGCR8	Negative	Poor prognosis	–	Promoting growth and proliferation	2021	(21)
		BTRC	Positive	Poor prognosis	NF- κ B	Promoting migration and invasion	2022	(22)
		miR-545-3p/circPRKCI	Negative/positive	Poor prognosis, advanced pTNM stage, larger tumor sizes, positive lymph node metastasis	PI3K/AKT	Promoting proliferation and migration	2022	(23)
NSCLC	Upregulated	LATS1	Negative	Poor prognosis, advanced pTNM stage, positive lymph node metastasis	Hippo	Promoting proliferation and invasion	2021	(12)
Glioma	Upregulated	ENO1, Homer3	Positive	Advanced pTNM stage	PI3K/Akt	Promoting growth, proliferation, cell cycle, migration and tumorigenic	2018	(14)
Gastric cancer	Upregulated	LATS2	Negative	Poor prognosis	Hippo	Promoting migration	2021	(15)
cSCC	Upregulated	YAP	Positive	–	Adherens junction	Promoting growth, proliferation Inhibiting differentiation	2017	(24)
HCC	Upregulated	miR-485-5p	Negative	–	Wnt/ β -catenin	Promoting proliferation, migration and invasion Inhibiting apoptosis	2020	(25)

WBP2, WW domain binding protein 2; NSCLC, non-small cell lung carcinoma; cSCC, cutaneous squamous cell carcinoma; HCC, hepatocellular carcinoma; ER, estrogen receptor; TAZ, transcriptional coactivator with PDZ-binding motif; ITCH, itchy E3 ubiquitin protein ligase; HER2, human epidermal growth factor receptor 2; DGCR8, DiGeorge Critical Region 8; BTRC, beta-transducin repeat containing E3 ubiquitin protein ligase; ENO1, α -enolase; Homer3, homer protein homolog 3; LATS1/2, large tumor suppressor kinase 1/2; YAP, Yes-associated protein; pTNM, pathologic tumor-node-metastasis; EGFR, epidermal growth factor receptor; PI3K, phosphatidylinositol 3-kinase; Akt/PKB, protein kinase B; NF- κ B, nuclear factor kappa B.

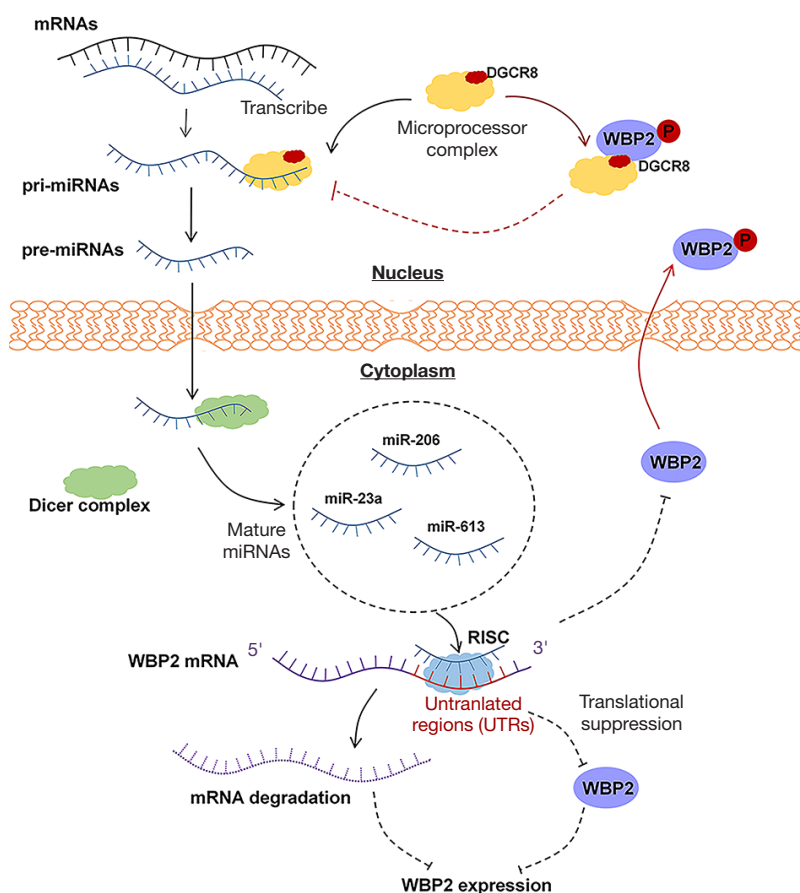


Figure 2 The process of mutual regulation between miRNAs and WBP2 in breast cancer. Black lines indicate the formation process of miRNAs and the inhibitory process of miRNAs on WBP2. In the nucleus, pri-miRNAs are first transcribed, followed by trimming at the microprocessor complex to engender the pre-miRNAs. Then pre-miRNAs are transferred from the nucleus to the cytoplasm and eventually synthesized into mature miRNAs by processing the Dicer complex, like miR-206, miR-23a, and miR-613. They bind to the 3' UTRs of WBP2 mRNA with the help of the RISC, thereby boosting WBP2 mRNA degradation or inhibiting the protein translation process. Red lines represent the reverse regulation of the miRNA biogenesis process by WBP2. DGCR8 is an important component of the microprocessor complex. By physically binding to DGCR8, WBP2 suppresses the activity of the microprocessor complex, thus inhibiting the biogenesis process of miRNAs and indirectly inhibiting the regulatory effect of miRNAs on WBP2. mRNA, messenger RNA; miRNA, microRNA; WBP2, WW domain binding protein 2; pri-miRNAs, primary miRNAs; pre-miRNAs, precursor miRNAs; 3' UTRs, 3' untranslated regions; RISC, RNA-induced silencing complex; P, tyrosine phosphorylation sites; DGCR8, DiGeorge Critical Region 8.

TNBC tissues and cell lines and localized mainly in the cytoplasm (23). By acting as a sponge for miR-545-3p, circPRKCI has been shown to indirectly upregulate WBP2 and accelerate the proliferation and migration of TNBC *in vitro* and *in vivo* (23). This is the only study to verify that circRNAs are involved in the regulation of WBP2 so far.

Long non-coding RNAs (lncRNAs)

lncRNAs are a class of ncRNAs longer than 200 nt, involved in regulating gene expression and multiple cellular

processes. Although no lncRNA involvement has been reported in the regulation of WBP2, it has been shown that lncRNAs are involved in regulating WBP2-related miRNAs. For example, lncRNA NEAT1 downregulation of miR-23a-3p expression (41) and lncRNA UCA1 downregulation of miR-613 expression (42) both contribute to paclitaxel resistance in breast cancer; lncRNA UCA1 and FTH1P3 promoted breast cancer proliferation and drug resistance by regulating miR-206 (43,44); lncRNA DSCR8 and LOC554202 acted as molecular sponges of miR-485-5p

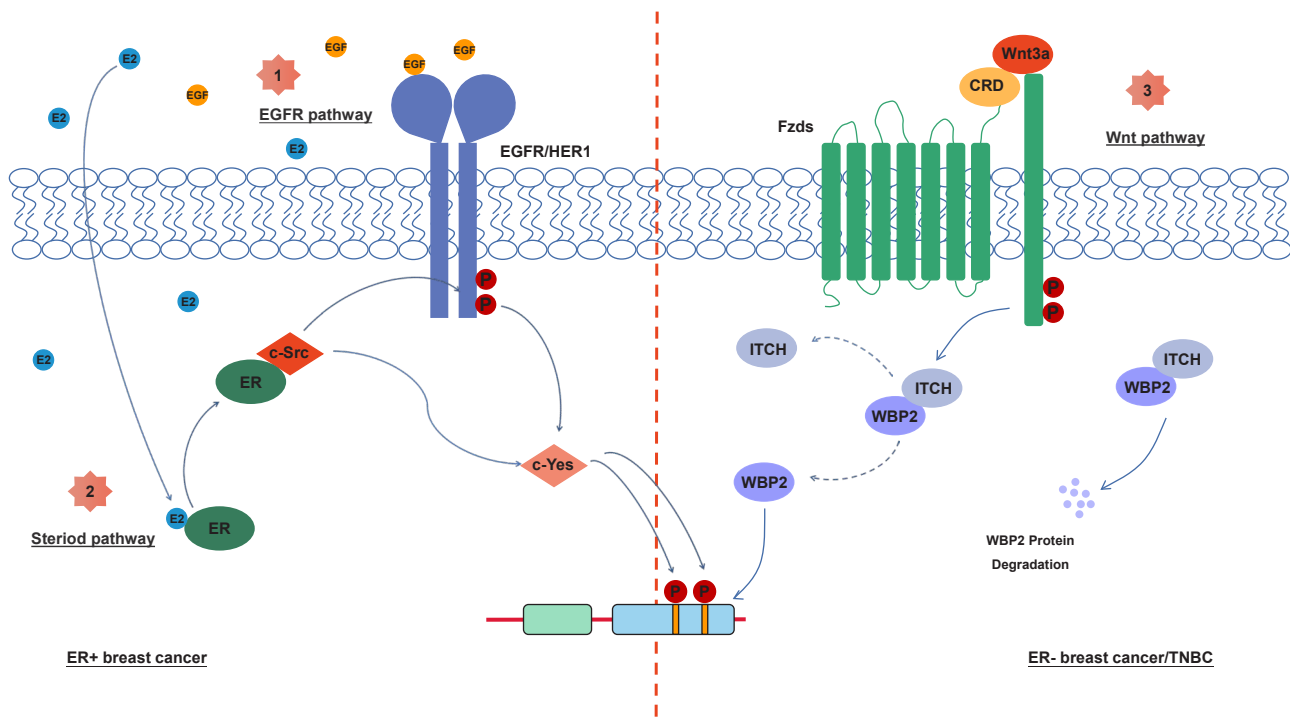


Figure 3 Three tyrosine phosphorylation activation pathways of WBP2. The solid line indicates promotion, and the dotted line indicates inhibition. [1,2] EGF and E2 activated c-Src and c-Yes via the EGFR and steroid signaling pathways, respectively, and then further stimulated the Tyr192 and Tyr231 site activation of WBP2 to enable the tyrosine phosphorylation of WBP2. These 2 phosphorylation pathways are commonly present in ER-positive breast cancer. [3] Wnt3a is a crucial signaling molecule of the Wnt pathway, which binds to Fzds to prevent ITCH from binding to WBP2. This improved the stability of the WBP2 protein and contributed to tyrosine phosphorylation. WBP2 protein phosphorylation of Wnt signaling pathway regulation usually occurs in ER-negative breast cancer or TNBC. WBP2, WW domain binding protein 2; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; Tyr192, tyrosine 192; ER, estrogen receptor; Fzds, Frizzleds; ITCH, itchy E3 ubiquitin-protein ligase; TNBC, triple-negative breast cancer; P, tyrosine phosphorylation sites; CRD, cysteine-rich domain; Wnt3a, Wnt family member 3a.

to promote HCC progression (45,46); and so on. These findings are potential directions for lncRNA involvement in WBP2 regulation. Perfecting these studies will benefit to elucidate the mechanistic network of lncRNAs involved in WBP2 regulation.

Post-translational regulation of WBP2

Post-translational modification of proteins is an important step in achieving gene expression, which includes phosphorylation, ubiquitination, and acetylation.

Tyrosine phosphorylation

Tyrosine phosphorylation was identified as the earliest form of post-translational modification of WBP2 (47). WBP2

is tyrosine phosphorylated and is driven to the nucleus by other molecules. High nuclear WBP2 levels have been shown to predict strong tumor aggressiveness and poor prognosis (10). Therefore, it is generally accepted that tyrosine phosphorylation, as a functional switch of WBP2, is important in cancer progression. We mainly summarize 3 pathways of tyrosine phosphorylation activation of WBP2, namely direct activation of epidermal growth factor receptor (EGFR) via EGF, crosstalk of estradiol (E2) and progesterone (P4) with EGFR, and mediation by Wnt ligands (*Figure 3*).

Direct activation of EGFR via EGF

In ER-positive breast cancer, EGFR signaling pathways activate WBP2 tyrosine phosphorylation (10). Both c-Src and c-Yes mediate tyrosine phosphorylation of WBP2 through Tyr192 and Tyr231. Unlike c-Src, c-Yes-induced

WBP2 tyrosine phosphorylation was determined by the activation of EGFR (*Figure 2*). C-Src may function both upstream and downstream of the EGFR during tyrosine phosphorylation of WBP2.

Crosstalk of E2 and P4 with EGFR

EGFR activation was caused by E2 and P4 crosstalk (10). E2 and P4 not only activate the proliferation of breast cancer cells via the nuclear receptor pathway but also have complex signaling communication processes with membrane receptors. Progesterone receptor membrane component 1 (PGRMC1) is overexpressed in both ER-positive and TNBCs (48). It has been shown to interact with the plasma membrane EGFR and increased and stabilized the latter levels (49). E2 and P4 could regulate PGRMC1 expression and then rapidly activate the EGFR pathway downstream of PGRMC1, boosting breast cancer cell proliferation (50). In addition, research has shown that E2 uses the classical steroid signaling pathway to act via ER with c-Src, further stimulating the cleavage and discharge of heparin-binding epidermal growth factor-like growth factor (HB-EGF) (51,52). HB-EGF then activates the EGFR signaling pathway by binding to EGFR via a similar domain to EGF, eventually promoting the phosphorylation of WBP2.

Mediation by Wnt ligands

Different from the EGFR pathway, the Wnt pathway is likely to be the most dominant way for TNBC missing ER expression to mediate tyrosine phosphorylation of WBP2. It is facilitated by Wnt family member 3a disruption of ITCH and WBP2 binding to promote WBP2 protein stability, followed by WBP2 binding to β -catenin to drive transcription mediated by T cell factor (TCF) (13).

Ubiquitination

Protein ubiquitination is another post-translational modification of WBP2 and is an enzymatic reaction. The ubiquitinated proteins are eventually identified and degraded by the proteasome to stabilize the intracellular environment and avert the occurrence of cancer (53). An article reviewed the ubiquitinated substrates of ITCH in various malignancies, including WBP2 (54). ITCH belongs to the HECT-type neuronally expressed developmentally downregulated 4 (NEDD4) family and contains 4 WW domains. It functions as a tumor suppressor in the Wnt signaling pathway of breast cancer, recognizing and degrading WBP2 protein by the PY-WW region (13). The

degradation of WBP2 by ITCH could not be completely abolished by proteasome inhibitors, thus suggesting that ITCH may have other modalities mediating the downregulation of WBP2 than by ubiquitination. WWP2, another member of the NEDD4 family, also has a hand in adjusting the ubiquitination of WBP2 through the WW domain (55). Hence, WBP2 may be a good ubiquitination substrate for the NEDD4 family. However, whether other members of this family, such as WW domain-containing E3 ubiquitin-protein ligase 1 and NEDD4, can regulate the ubiquitination of WBP2 protein remains to be investigated.

Signaling pathways of WBP2

The WBP2 protein exerts oncogenic functions by directly participating in Wnt, Hippo, EGFR, and other pathways.

Wnt signaling pathway

The Wnt pathway plays an important role in antitumor response inhibition (56,57). Any abnormalities in this pathway may lead to pathological changes in the body, such as the aberrant initiation of the Wnt pathway in TNBC is imperative for migration and metastasis (58-60).

WBP2 is an important regulator of gene transcription induced by the Wnt pathway; WBP2 regulates nearly 80% of Wnt target genes in TNBC (58). WBP2 ordinarily works as a bridge between the Wnt pathway and other signaling pathways to promote breast cancer progression. Wnt signaling, for example, has been shown to protect WBP2 from ubiquitination degradation of ITCH under Wnt 3a and to drive WBP2 into the nucleus to enhance β -catenin/TCF-mediated transcription, thereby promoting breast cancer progression (13). Indeed, this process also involves the Hippo pathway that mediates the competitive binding of YAP/TAZ to WBP2 and the EGFR signaling pathway that invokes the tyrosine phosphorylation of WBP2 (13). Alternatively, the Wnt and c-Jun N-terminal kinase signaling pathways collaborate to promote TNBC growth via the junction of the WBP2 (58). Wnt cooperates with the Hippo pathway to regulate WBP2 (61-63). Lim *et al.* predicted that Wnt signaling could downregulate ER α expression to regulate ER signaling when mediated by WBP2 (10). It was advocated that WBP2-mediated breast cancer prefers to rely on the Wnt pathway as opposed to the ER pathway. In conclusion, the Wnt signaling pathway is the backbone of WBP2-mediated breast cancer progression.

As the activation of the Wnt pathway in breast cancer is

more complex and frequently implicates the dual effects of both canonical and non-canonical Wnt pathways (64–66), it is uncertain whether the Wnt pathway can be successfully used in breast cancer treatment. Gratifyingly, researchers have mentioned that Wnt pathway-targeted therapy is expected to convert into a true treatment approach (67). Thus, it cannot be ignored that the potential of the Wnt signaling pathway to be a therapeutic target for WBP2-positive breast cancer.

Hippo signaling pathway

The Hippo signaling pathway is committed to suppressing cell proliferation, promoting apoptosis, and regulating the cell cycle (68–70). The core components of Hippo are mainly constitutive of mammalian STE20-like protein kinase 1/2 (MST1/2), LATS1/2, and their adaptor proteins Salvador homologue 1 (SAV1) and MOB kinase activator 1A/B. They inhibit transcriptional coactivator activity of downstream YAP/TAZ through a series of protein cascades, thereby inhibiting *in vitro* transformation and *in vivo* tumorigenesis (71,72). Oncogenic factor WBP2 is mutually regulated with the Hippo pathway to promote or restrict cancer progression.

WBP2 inhibits the Hippo pathway in 2 ways

WBP2 as a transcriptional coactivator of YAP/TAZ

The synergy between WBP2 and YAP was initially identified by a functional screen using the complementary DNA (cDNA) expression library (3). WBP2 collaborates with YAP via the PY-WW region to drive YAP transcriptional activity, enhancing the proliferative advantage of YAP in multiple cellular systems, including breast cancer cells (19,68). Moreover, WBP2 cooperates with TAZ in a similar way to YAP to promote TAZ-mediated breast cell transformation (11). Interestingly, p73 was found to competitively bind to YAP with WBP2, because the PY motif contained by p73 is similar to that of WBP2 (73). In contrast to previously identified oncogenic functions, YAP exerts a tumor suppressor effect by binding p73 to promote its transcriptional activity and enhance the induction of apoptosis (74,75). Studying how WBP2 interferes with the tumor suppressive effect of YAP-p73 is important for the exploitation of clinical WBP2-targeted drugs.

WBP2 as an adaptor of LATS1/2

LATS1/2 phosphorylation activation is significant for the proper functioning and maintenance of the Hippo pathway. The WBP2 inhibition of LATS1/2 phosphorylation inhibits the upstream Hippo pathway in a way not directly

dependent on YAP.

In gastric cancer, WBP2 is directly bound to LATS2, lacking the WW domain, to constrain the phosphorylation of the Hippo pathway (15). Pull-down assays have demonstrated that WBP2 and LATS2 may function by binding to their respective C-terminal regions (15), providing evidence that WBP2 exerts functional activity with non-WW structural domain dependence. Of course, we cannot rule out the possibility that other molecular signals play an indirect role. In addition to this, it should be considered that WBP2 may have a stabilizing effect on the inactive conformation of LATS2 or that WBP2 acts as a linker protein for LATS2 to non-allosterically inhibit its activity.

In non-small cell lung cancer (NSCLC), WBP2 competes with LATS1 to bind the WW domain of WWC3, inhibits the formation of the LATS1-WWC3 complex, and leads to the downregulation of LATS1 phosphorylation (12). Researchers have summarized the signaling axis of MST1/2-SAV1-WWC1/2/3-LATS1/2-YAP/TAZ (76). As a tumor suppressor in human cancers (77), WWC proteins with a double WW domain should also be important constituents of the Hippo pathway. *WWC1* deficiency has been linked to TNBC cell metastasis in multiple publications (78,79) and has been shown to predict poor prognosis (80). It is regrettable that *WWC1/2*, which is closely associated with breast cancer, has not been reported to interact with WBP2. Future studies can be conducted in this direction to enrich the mechanistic studies of WBP2.

Hippo pathway regulates WBP2 in 2 ways

MST-Dicer signaling axis

MST is required for the expression of Dicer, an enzyme required for pre-miRNA processing. The novel MST-Dicer axis downregulates WBP2 and conspicuously suppresses the WBP2-mediated cell growth and proliferation effects via miR-23a (38). The whole process does not involve the downstream LATS of the MST. Another study demonstrated that LATS could downregulate WBP2 in an MST-independent manner, but was less effective than the MST (81). Furthermore, YAP and TAZ downstream have been shown to actively adjust Dicer expression post-transcriptionally via Let-7 (82), implying that YAP/TAZ is also indirectly engaged in WBP2 regulation by the MST/Dicer axis.

ITCH-mediated proteasomal degradation

ITCH is considered an inhibitor of the Hippo pathway because it mediates LATS1 degradation (83,84).

However, the WBP2 degradation induced by ITCH as a tumor suppressor could be reversed by YAP/TAZ overexpression (13). This is because YAP/TAZ and ITCH compete with the PY motif of WBP2. Not only that, the WBP2-ITCH complex can also be inhibited by other signaling pathways such as Wnt and EGFR (13), which further enhances the complexity of the WBP2/Hippo network. More research into the functions of ITCH in different pathways may provide broader evidence support for interactions in the WBP2 and Hippo pathways.

EGFR signaling pathway

The EGFR signaling pathway is a major pathway for cell survival and has been linked to drug resistance (85,86). Positive EGFR expression is frequently associated with poor prognosis of the tumors, including TNBC (87,88).

WBP2 is a true tyrosine phosphorylation target of the EGFR signaling pathway. EGF exhibits a similar tendency to the tyrosine phosphorylation pattern of the WBP2 protein in breast cancer cells (47). Similar to Wnt, EGFR is involved in regulating the protein stability of WBP2 (47). In addition, it has been discovered that the downregulation of WBP2 reduces the expression of the EGFR proteins, as well as pivotal proteins in the EGFR pathway (19). Given the role of WBP2 on the EGFR pathway, further development of combined inhibitors of WBP2 and EGFR pathways is perhaps an effective medicinal strategy for ER-negative breast cancer.

Other pathways

Except for the 3 main signaling pathways studied above, other pathways have also been implicated in the carcinogenic effects of WBP2. For example, the downregulation of WBP2 can reduce the expression of key proteins in the PI3K/AKT pathway and affect the growth and development of breast cancer cells (19). ENO1 and glycolytic virtue are regulated by WBP2 through the ENO1-PI3K/Akt pathway, thus being charged with the occurrence and advancement of glioma (14). WBP2 overexpression induces the adenosine monophosphate-activated protein kinase β 1 (AMPK β 1) phosphorylation and activates the AMPK pathway to reduce fat deposition, which provides a new direction for the therapy of non-alcoholic fatty liver disease and insulin resistance (29). Moreover, WBP2 can maintain the mRNA stability of beta-transducin repeat containing E3 ubiquitin-protein ligase in TNBC,

resulting in the ubiquitination and degradation of nuclear factor kappa B inhibitor α , and ultimately promoting the invasion and migration induced by WBP2 in TNBC (22).

Taken together, WBP2 is the node that links multiple signaling pathways. WBP2 is activated in response to crosstalk of multiple pathways including ER, EGFR, Wnt and Hippo. Phosphorylated WBP2 entry into the nucleus promotes transcription of oncogenes, thereby promoting cancer progression. The entry of WBP2 into the nucleus is also regulated by phosphorylated WW-containing oxidoreductase (WWOX), which hinders the entry of WBP2 by binding to the PY motif of WBP2, thereby inhibiting WBP2-mediated transcriptional function (5,8) (Figure 4). WBP2 is probably an innovative biomarker and a potential therapeutic target for breast cancer.

Nuclear WBP2 protein is a potential indicator for the diagnosis and prognosis of breast cancer

WBP2 expression is inconsistent at the protein and mRNA levels in different cancers, as shown by the bioinformatic analysis (27) and the experimental results (13). Especially in hormone-dependent cancers such as breast cancer, high WBP2 protein levels are more common than high WBP2 mRNA expression. Moreover, the high levels of WBP2 protein are more likely present in aggressive breast cancer cell lines and clinical tissues (13). Lim *et al.* summarized that WBP2 promotes cancer phenotypes in breast cancer cell lines (89). Chen *et al.* found that WBP2 overexpression caused increased chemotherapy drug resistance in MCF-7 cells (6). These studies indicate that overexpression of WBP2 promotes malignant progression of breast cancer (Figure 5A,5B).

Among the proteins encoded by *WBP2*, nuclear WBP2 is considered the main functional form of WBP2 after its activation. Lim *et al.* further analyzed the WBP2 protein levels in the cytoplasm and nucleus by immunohistochemistry and confocal microscopy and found a more significant increase in WBP2 protein in the nucleus compared to normal tissue (13). Moreover, the expression of nuclear WBP2 was negatively correlated with overall survival and disease-free survival, suggesting a worse prognosis for patients with high nuclear WBP2 protein levels (Figure 5C).

In summary, we believe that nuclear WBP2 protein is a vital indicator for the diagnosis and prediction of breast cancer progression. Nonetheless, the detection of the WBP2 protein still requires additional assays for a joint

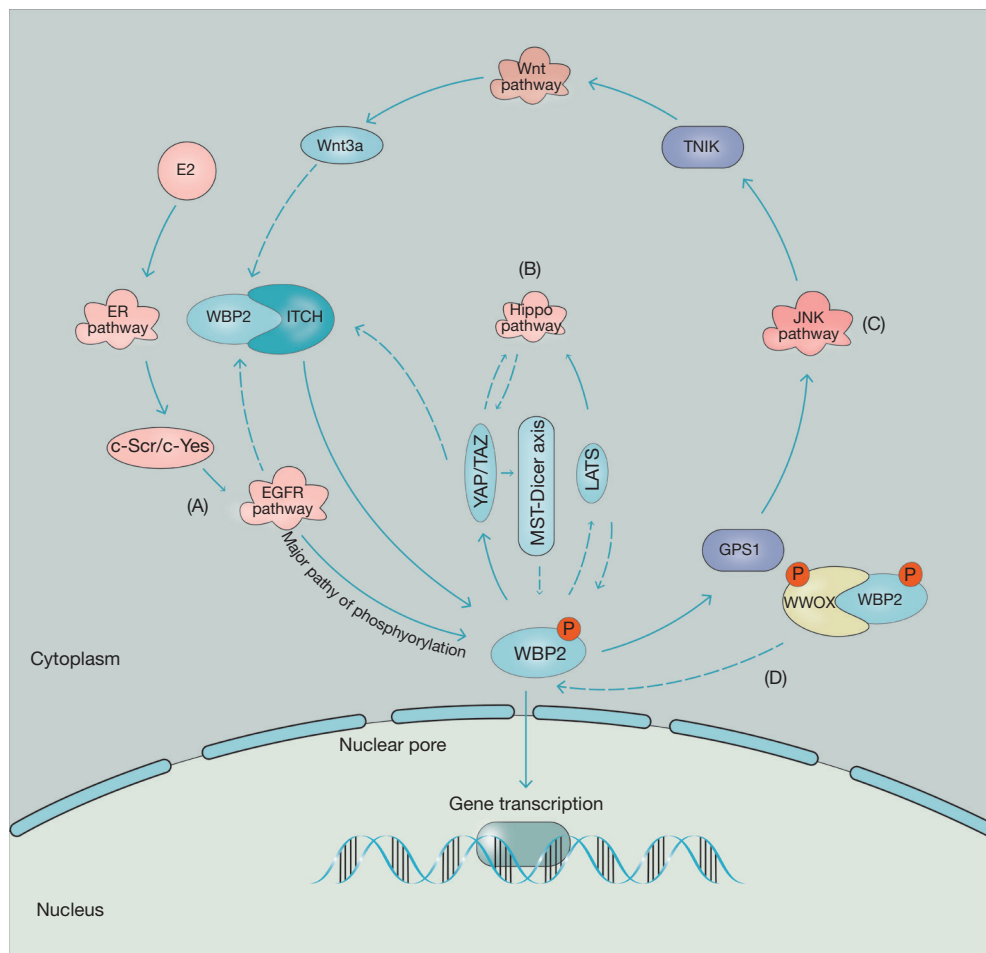


Figure 4 WBP2 functions as a key node crosstalks ER, EGFR, Wnt and Hippo signaling pathways. The solid line indicates promotion, and the dotted line indicates inhibition. ITCH inhibits its phosphorylation by binding to WBP2. However, the formation of the ITCH-WBP2 complex can be inhibited by the YAP/TAZ (Hippo pathway), Wnt, and EGFR pathways, which leads to the release and phosphorylation activation of WBP2. (A) The EGFR pathway activated by E2 crosstalk is the main phosphorylation activation pathway of WBP2. (B) WBP2 represses the Hippo pathway by promoting YAP/TAZ or inhibiting LATS transcriptional activity, and conversely, the Hippo pathway can inhibit WBP2 activation. (C) WBP2 can also activate the Wnt signaling pathway through the GPS1/JNK/TNIK signaling axis, creating a positive feedback loop on WBP2 activation. (D) Phosphorylated WWOX binds to WBP2 and inhibits WBP2 entry into the nucleus, resulting in the repression of WBP2-mediated transcriptional function. WBP2, WW domain binding protein 2; E2, estradiol; ER, estrogen receptor; ITCH, itchy E3 ubiquitin-protein ligase; EGFR, epidermal growth factor receptor; YAP, Yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; LATS, large tumor suppressor kinase; MST, mammalian STE20-like protein kinase; Wnt3a, Wnt family member 3a; GPS1, G protein pathway suppressor 1; JNK, c-Jun N-terminal kinase; TNIK, TRAF2- and NCK-interacting kinase; WWOX, WW-containing oxidoreductase; P, tyrosine phosphorylation sites.

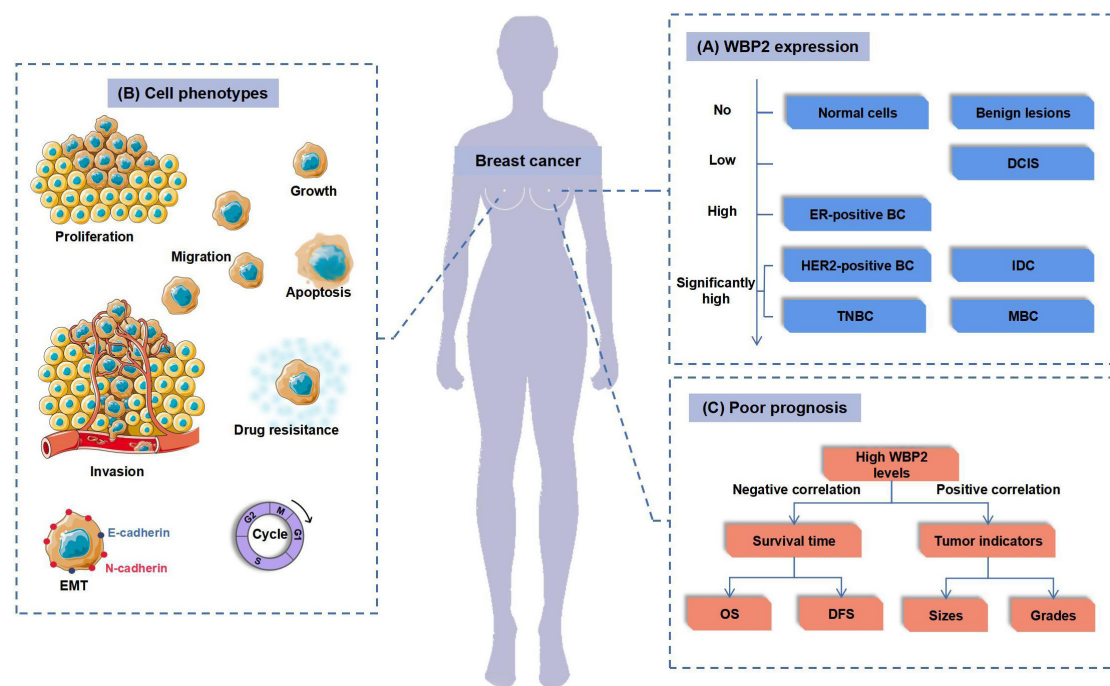


Figure 5 Overexpression of WBP2 promotes the malignant progression of breast cancer and poor patient survival. (A) WBP2 expression is related to malignant grading and different subtypes of breast cancer: WBP2 is hardly expressed in normal cells or benign lesions. With increasing degrees of malignancy, WBP2 expression is upregulated. For example, WBP2 expression starts to occur in DCIS and is greatly abundant in IDC and MBC. WBP2 was found to be significantly more abundant in HER2-positive breast cancer and TNBC than in ER-positive breast cancer in different subtypes of breast cancer. (B) WBP2 is related to a wide variety of cell phenotypes, like proliferation, cell growth, migration, invasion, EMT, cell cycle, and drug resistance. (C) WBP2 is closely tied with poor prognosis: WBP2 is positively relevant to tumor size and cancer grade and is negatively linked to OS and DFS. EMT, epithelial-mesenchymal transition; M, mitotic phase; S, DNA synthesis phase; G1, gap 1 phase; G2, gap 2 phase; WBP2, WW domain binding protein 2; ER, estrogen receptor; BC, breast cancer; TNBC, triple negative breast cancer; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; MBC, metastatic breast cancer; OS, overall survival; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2.

evaluation to improve the reliability of its applications, such as immunofluorescence, immunochemical cytochemical techniques, etc.

WBP2 and breast cancer therapy

Relationships between WBP2 and drug resistance in breast cancer

The high morbidity and mortality rates of breast cancer have long made its treatment a focus of clinicians' attention. Drug tolerance is now the greatest challenge faced by clinicians. Since WBP2 has an indispensable role in inducing drug resistance in breast cancer, we hope to find new opportunities to develop effective targeted therapeutics from the link of WBP2 to breast cancer drug resistance.

In ER-positive breast cancer

WBP2 is associated with doxorubicin resistance in ER-positive breast cancer. The WBP2 protein was found to be poorly expressed in the ER-positive MCF-7, but highly expressed in the MCF-7 doxorubicin-resistant strains. This differential expression was not appropriate for the ER-negative MDA-MB-231 cell line (6). This indicates that the high expression of WBP2 produced by doxorubicin-resistant cells is related to the positive state of ER. Prolonged stimulation with doxorubicin induces high expression of WBP2 in ER-positive breast cancer cells, and the up-regulation or down-regulation of WBP2 results in altered doxorubicin sensitivity in ER-positive breast cancer (6). This suggests that WBP2 has a potential role in inducing doxorubicin resistance in ER-positive breast cancer. Chen *et al.* found that WBP2 is directly associated

with multidrug resistance gene 1 (MDR1) and demonstrated that WBP2 directly binds to ER α to activate downstream MDR1, which leads to doxorubicin efflux and resistance in ER-positive breast cancer (6). These findings suggest that the WBP2-ER α -MDR1 axis may be a new mechanism of chemotherapy resistance in ER-positive breast cancer.

Upregulation of WBP2 is also closely linked to tamoxifen resistance, the most commonly used chemotherapeutic in ER-positive breast cancer (90). It can compete with estrogen to bind ER, hence restraining the conventional ER transcriptional program (91). However, tamoxifen has been shown to fail to prevent WBP2-induced breast cancer growth and proliferation (10). Ren *et al.* suggested that ER-positive breast cancer alters tamoxifen sensitivity by adjusting G1/S progression through the miR-206/WBP2 axis (18).

In HER2-positive breast cancer

As we all know, one of the first-line drugs for HER2-positive breast cancer is trastuzumab, but not all patients have been shown to benefit from it (92). It is probably because the response of breast cancer to trastuzumab does individually rely not only on HER2 expression but also on other biomarkers such as WBP2 (20). Kang *et al.* showed that HER2-positive breast cancer with high WBP2 levels is more effective on trastuzumab (20). It might be due to the combined amplification of *HER2* and *WBP2* on the q-arm of chromosome 17 and the activation of tyrosine phosphorylation of WBP2 by HER2 in response to the crosstalk of the EGFR signaling pathway. This is not surprising, as it has been found that heterodimerization of EGFR and HER2 occurs in the presence of EGF (47). The above illustrates that WBP2 might be a valid predictor in HER2-positive breast cancer treated with trastuzumab. Moreover, WBP2 co-expression with HER2 in breast cancer patients was connected to a worse prognosis than HER2 expression alone (20). This suggests that WBP2 remains a hazard factor for HER2-positive breast cancer.

In conclusion, WBP2 involves multiple drug resistance mechanisms and is probably a valid target for overcoming multidrug resistance in breast cancer. Although no studies have reported that WBP2 is involved in the chemotherapeutic resistance of TNBC, the high expression of WBP2 in ER-negative MDA-MB-231 may be an important hint (6). If the mechanism of drug resistance in TNBC expressing high WBP2 levels is investigated, it will help to elucidate the role of other hormone-independent factors in inducing drug resistance by WBP2.

Immunotherapy of WBP2 in breast cancer

WBP2 is also being mined as a potential direction for immunotherapy. A study on the proliferative activity of WBP2 promoting CD4⁺ T cells was published in 2020 (31). CD4⁺ T cells, which are not fully appreciated in immunotherapy, have great potential for immunotherapy. CD4⁺ T cells can directly recognize major histocompatibility complex class II antigens that are expressed only by a minority of tumor cells and produce killing effects (93). There is clinical evidence for the involvement of CD4⁺ T cells in antitumor immunity (94). The experiment demonstrated that reduced stability of WBP2 hindered the entry of CD4⁺ T cells into the S phase. Moreover, the degradation effect of ITCH on WBP2 in CD4⁺ cells helped to prevent the excessive proliferation of immune cells. Although the finding that WBP2 is important in regulating immune cells is encouraging, it is still difficult to successfully apply WBP2 to immunotherapy. The specific functions of WBP2 in CD4⁺ T cell subsets or other immune cells remain to be explored.

Potential synergistic treatments for breast cancer

The rise of immunological biological agents and molecularly targeted agents has expanded the scope of therapeutic options in clinical patients. From 2010 to 2020, the Food and Drug Administration (FDA) approved 26 drug indications for the treatment of clinical metastatic breast cancer, of which only one was for chemotherapy and the remaining 25 were for targeted therapies and immunotherapy (95). The advent of targeted therapies has made it possible to extend the lives of more advanced breast cancer patients.

As WBP2 induces multiple drug resistance in breast cancer, we propose that targeting WBP2 may be a feasible therapeutic strategy, such as WBP2 protein inhibitors targeting the PY motif. Given the limitations of monotherapy, combination therapy is considered to achieve better anticancer outcomes. This is because (I) combination therapies can synergistically target cancer from multiple pathways, addressing the issue of drug unavailability due to tumor heterogeneity and lowering the likelihood of cancer cells developing drug resistance (96). (II) Combination therapies can also mitigate the toxicological response caused by high-dose monotherapy (97). (III) FDA-approved drugs can be used in combination therapies to expedite FDA approval and lower drug discovery and validation costs (95).

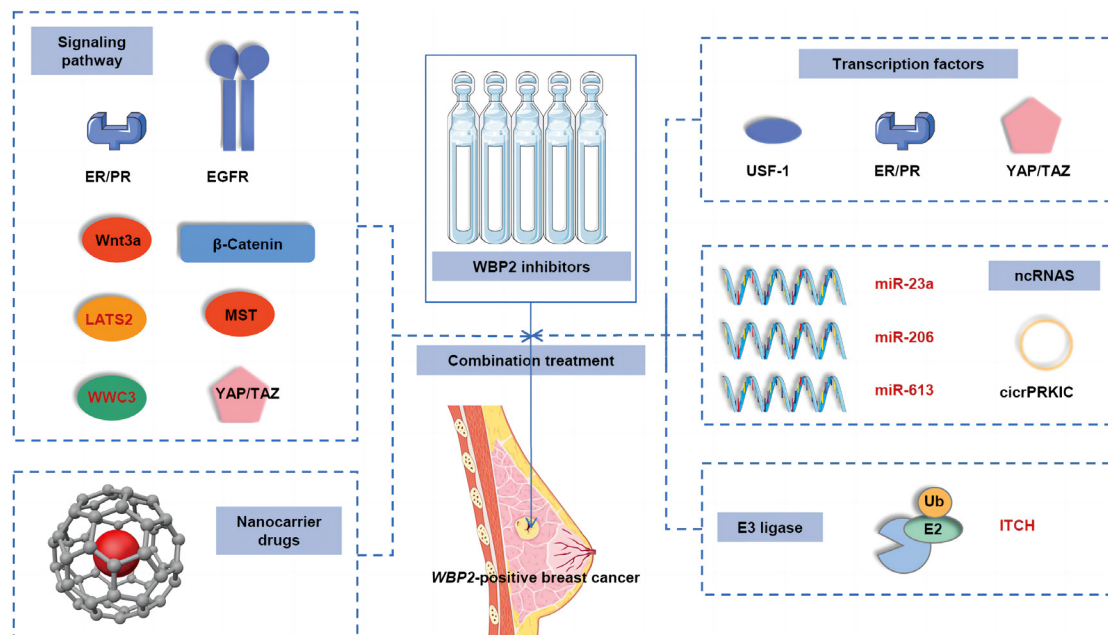


Figure 6 Potential combination treatment of WBP2 for breast cancer. Because WBP2 is subject to multiple regulatory and regulated effects, we can combine WBP2 protein inhibitors with these drugs from the perspective of molecular interactions. The black font represents signaling molecules that act in concert with WBP2 and can be used in combination with their inhibitors. Red represents signaling molecules that have opposite effects on WBP2 and can be used in combination with their activators. WBP2, WW domain binding protein 2; ER, estrogen receptor; PR, progesterone receptor; EGFR, epidermal growth factor receptor; Wnt3a, Wnt family member 3a; LATS2, large tumor suppressor kinase 2; MST, mammalian STE20-like protein kinase; WWC3, WW and C2 domain-containing protein-3; YAP, Yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; ncRNAs, non-coding RNAs; ITCH, itchy E3 ubiquitin-protein ligase; Ub, ubiquitin; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; USF-1, upstream transcription factor 1.

Therefore, combination therapy is closer to the concept of precision medicine and helps to achieve the goal of individualized therapy.

As shown in *Figure 6*, we listed 5 directions of combination treatment with WBP2 protein inhibitors: (I) combined targeting of transcription factors that bind to WBP2 to inhibit WBP2 function at the transcriptional levels. (II) Combined use of miRNA agonists and MST/Dicer agonists to promote miRNA biogenesis to inhibit WBP2 activity at the post-transcriptional level. (III) Combined application of E3 ligase activators such as ITCH, which binds tightly to WBP2 and inhibits its phosphorylation activation. (IV) In combination with inhibitors of signaling pathways closely related to WBP2 phosphorylation activation. (V) Appropriate application of novel materials improves the efficiency of drug targeting. Such as new nanocarrier drugs (98), which can be effectively delivered to the tissue site, so the drug dose and frequency of use can be reduced accordingly, thus reducing the toxic

reactions of patients.

Conclusions

The oncogenic role of *WBP2* in human cancers, especially breast cancer, is gradually being revealed. *WBP2* functions as an oncogene, regulating breast cancer initiation and development. It was first discovered as a ligand for YAP (3), gradually revealed as a transcriptional coactivator of ER/PR (4,5), then as a new tyrosine kinase substrate in the EGFR pathway (47), and shown to act as a transcriptional activator of YAP/TAZ (11,19), and LATS1/2 (15) phosphorylation inhibitor in the hippo pathway, as a bridge identity linking the Wnt pathway and other pathways (13) and so on. WBP2, under the transcriptional regulation of transcription factors (30) and ncRNAs (18,21,25,38), as well as the post-translational modification of ITCH (13), causes a differential expression of mRNA and protein. Considering the main active form of WBP2,

we propose that nuclear WBP2 protein as the standard represents the level of WBP2 and consider nuclear WBP2 as an important indicator for early diagnosis and prognostic monitoring of breast cancer.

From the protein structure of WBP2, the functions of the 2 phosphorylation sites and 3 PY motifs in the C-terminal region are well defined. However, we found that there may be other functional regions at the C-terminus, as WBP2 can interact with proteins without the WW domain. It indicates that the non-PY region at the C-terminus of WBP2 is functioning, but the exact location needs to be explored in depth. In addition, in ER-positive breast cancer, hormones play a very important role in the activation of WBP2 phosphorylation. However, in other hormonal cancers where WBP2 is overexpressed, such as ovarian cancer and prostate cancer, it remains to be explored whether the activation of WBP2 is similarly regulated by hormonal effects.

Targeted therapies are often more precise than traditional chemotherapy in suppressing tumors and destroying tumor mechanisms. Tamoxifen (ER antagonist) and trastuzumab (HER2 antagonist), the first developed and most commonly used in breast cancer, were found to be insensitive to WBP2-overexpressed breast cancers. In this review, we found that, in addition to ER and EGFR pathways, WBP2 activation can also be regulated by Wnt and Hippo pathways. Therefore, we can consider the combination of other pathway inhibitors for the treatment of WBP2-positive breast cancer. The most direct approach is to formulate new targeted drugs against the active structural domain of WBP2, PY, to fundamentally inhibit the activation of WBP2.

Since only about 10% of the human genome can be the target of drugs (99), it remains to be seen whether *WBP2* can be used as a drug-targeting molecule. In the future, the combination therapy strategies proposed will help accelerate the development and approval of WBP2-associated drugs. We hope that more and more signaling molecules can be discovered to clarify how *WBP2* functions as an oncogene. By testing the gene expression profile of WBP2-positive breast cancer, it will be of great importance to establish a unique molecular profile and customize a personalized therapeutic regimen. This will facilitate more effective treatment and fewer complications for WBP2-positive breast cancer patients. In the future, we may be able to achieve precise treatment of WBP2-positive breast cancer through local biopsy and before and after therapy with WBP2 protein testing.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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