Utilizing the Hippo pathway as a therapeutic target for combating endocrine-resistant breast cancer

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Abstract

Drug resistance is always a great obstacle in any endocrine therapy of breast cancer. Although the combination of endocrine therapy and targeted therapy has been shown to significantly improve prognosis, refractory endocrine resistance is still common. Dysregulation of the Hippo pathway is often related to the occurrence and the development of many tumors. Targeted therapies of this pathway have played important roles in the study of triple negative breast cancer (TNBC). Targeting the Hippo pathway in combination with chemotherapy or other targeted therapies has been shown to significantly improve specific antitumor effects and reduce cancer antidrug resistance. Further exploration has shown that the Hippo pathway is closely related to endocrine resistance, and it plays a “co-correlation point” role in numerous pathways involving endocrine resistance, including related pathways in breast cancer stem cells (BCSCs). Agents and miRNAs targeting the components of the Hippo pathway are expected to significantly enhance the sensitivity of breast cancer cells to endocrine therapy. This review initially explains the possible mechanism of the Hippo pathway in combating endocrine resistance, and it concludes by recommending endocrine therapy in combination with therapies targeting the Hippo pathway in the study of endocrine-resistant breast cancers.

Keywords: Hippo pathway, Breast cancer, Endocrine therapy, Endocrine resistance, Breast cancer stem cells, MicroRNA

Introduction

The incidence of breast cancer ranks first among all female malignancies [1]. Most breast cancers are surely estrogen receptor-positive (ER+) and can depend on estrogen for tumor cell growth. The major treatment strategy for endocrine therapies focused on ER+ breast cancer is estrogen deprivation. The current drugs to this end can be classed as aromatase inhibitors, selective estrogen receptor degraders, and selective estrogen receptor modulators. However, about one-third of patients still develop recurrence after long-term endocrine therapy [2]. Drug resistance to endocrine therapy has become a pivotal obstacle to treatment, although endocrine therapy is effective in reducing mortality and improving survival rates [3]. The reasons for drug resistance are multiple and complex, and they involve various molecules. Currently, targeted therapies combined with endocrine therapy have been shown to be effective for combating endocrine resistance, as illustrated in Table 1, which includes targets of Cyclin-dependent kinases (CDKs) 4 and 6, mammalian targets of rapamycin (mTOR) and phosphoinositide 3-kinase (PI3K). Their combination as first or second-line treatments for
hormone receptor-positive metastatic breast cancer has been recommended by AMA guidelines, which was corroborated by a network meta-analysis [4]. Unfortunately, the combination of CDK 4 and 6 inhibitors still does not completely overcome drug resistance [5, 6]. The Hippo pathway, a newly targeted pathway, has been found to be related to multiple malignancies and modulation of this pathway may be able to effectively overcome endocrine resistance. In this review, the therapeutic potential of the Hippo pathway in the promotion of endocrine therapy is addressed, which provides theoretical references for the design of further studies and clinical consequences.

Mechanism of endocrine resistance in breast carcinoma
The complex reasons of endocrine resistance involves the estrogen receptor (ER) pathway, the growth factor receptor (GFR) pathways, and the CDK 4 and 6 pathway, as well as epigenetic modification. In recent years, the interdependence between BCSCs and drug resistance has emerged, and it often involves BCSC-related pathways, offering new insight into endocrine resistance.

Refractory resistance facilitated by escaped BCSCs
BCSC-related markers, such as CD44+CD24−/low [12], ALDH [13], CD133 [14], Nanog [15], Sox2 [12], and Sox9 [16], were found to be enriched or positive in tamoxifen-resistant [12–16], letrozole-treated [17], and fulvestrant-treated cells [18]. The proportion of cells bearing stem cell markers in resistant cell line stronger increased than that of non-resistant [12]. On the one hand, dormant and self-renewal deficient BCSC populations are generated during long-term endocrine therapy, leading to endocrine resistance after these cells exit from metabolic

| Targets | Agents | Mechanism | References |
|---------|--------|-----------|------------|
| mTOR    | Everolimus | Generates a complex that inhibits the activation of mTOR | [7] |
| CDK4/6  | Palbociclib | Inhibits CDK4/6, allowing restoration of control of cell cycle | [8] |
|         | Ribociclib |                                                   | [9] |
|         | Abemaciclib |                                                  | [10] |
| PI3K    | Alpelisib | Specifically inhibits PI3Kα | [11] |

CDK cyclin-dependent kinase, mTOR mammalian target of rapamycin, PI3K phosphoinositide 3-kinase

Fig. 1 Illustration of preliminary mechanisms driving endocrine resistance in breast cancer. ER signaling drives cell growth in breast cancer. These driving forces convert from ER signaling to GFR signaling, with the interruption or the gradual reduction of ER signaling and the increase of GFR signaling. Interactions between GFR signaling and BCSC-related pathways will form stronger driving forces and lead to refractory breast cancer
| BCSC-related pathways | Association with BCSCs | Association with endocrine resistance |
|-----------------------|------------------------|--------------------------------------|
| EGR                   | +          | EGFR signals in response to endocrine resistance may mediate resistance to tamoxifen. |
| MAPK                  | +          | The MAPK pathway is involved in the regulation of BCSCs. |
| Wnt                   | +          | Wnt/β-catenin signaling increases the sensitivity of breast cancer cells to tamoxifen. |
| Hh                    | +          | The Hh pathway regulates BCSCs by increasing GLI expression and activity. |
| TGF-β                 | +          | TGF-β induces sphere-forming efficiency in MDA561 and BT474 cells, and inhibits the activity of BCSCs. |

**Table 2** Preliminary mechanisms of BCSC-related pathways associated with endocrine resistance

*Notes: All pathways are involved in the regulation of BCSCs. The MAPK pathway is activated by ERα36 in breast cancer cells, which leads to the activation of Wnt/β-catenin and Hh pathways. EGFR signals in response to endocrine resistance may mediate resistance to tamoxifen. TGF-β induces sphere-forming efficiency in MDA561 and BT474 cells, and inhibits the activity of BCSCs.*

**References:**

1. Chen et al. Cancer Cell Int. (2021) 21:306
2. ERα36-EGFR/HER2 pathway regulates the population of ALDH1 breast cancers and HER2 expression.
3. EGFR overexpression regulates the  CD24lowCD44high and  ALDH1 enriched population in breast cancer cell lines.
4. TGF-β and PI3K pathway activity with worse response in treatment of tamoxifen-resistant breast cancer.
5. Hypoxia induces sphere-forming efficiency in BCSCs.
6. Hypoxia-activated pathways enable BCSCs to everolimus resistance via MAPK pathway.
7. EGFR expression and HER-2 amplification are related with SDF-1–mediated stimulation of BCSC population.
dormancy [19]. On the other hand, ER activity affects the enrichment of BCSCs via mutations in the \textit{ESR1} gene (estrogen receptor-gene), including \textit{Y537N}, \textit{Y537S}, and \textit{D598G}, which are involved in ligand-independent activation of ER [20]. Moreover, ER-α36 [21], ERβ [22], and G protein-coupled estrogen receptor (GPER) [23] are all involved in the promotion or maintenance of breast cancer stem cell character. Moreover, BCSC populations are considered to be estrogen receptor negative (ER$^-$) and can regulate ER expression [24, 25], giving them the ability to generate ER$^+$ cells [26] or differentiate into cells that have lost ERα expression [27]. Therefore, the core reason for drug resistance is the stem cell behavior of breast cancers.

The interaction between ER signaling, GFR signaling, and BCSC-related pathways

BCSC-related pathways include the Hippo pathway, and those that signal via Hedgehog (Hh) signaling, transforming growth factor β (TGF-β) signaling, Notch signaling, PI3K/Akt/mTOR pathway, Wnt pathway, epidermal growth factor receptor (EGFR) pathway, ER signaling, and mitogen-activated protein kinase (MAPK) pathway. GFR signaling includes human epidermal growth factor receptor 2 (HER2) signaling, fibroblast growth factor receptor 1 (FGFR) signaling, and PI3K/Akt pathway, and they are three BCSC-related pathways. And other GFR signaling pathways are insulin-like growth factor 1 receptor (IGF-1R) signaling, MAPK signaling, and EGFR pathway. ER signaling is considered to be the main source of driving forces for the growth of ER$^+$ breast carcinomas. Changes in ER signaling are the first step for acquiring endocrine resistance, and this can include downregulation of ERα expression or loss of ERα expression caused by mutation or methylation of ERα-related genes [28]. These driving forces convert from ER signaling to GFR signaling [29, 30], as described in Fig. 1. The cross talk between GFR signaling and BCSC-related pathways may be the next step that leads to refractory resistance [28, 31, 32]. The preliminary relationship between part of BCSC-related pathways and endocrine resistance is diverse and complex, as illustrated in Table 2. And several signaling pathways of GFR are also BCSC-related pathways in this table. This reveals the dual roles of PI3K/Akt/mTOR, EGFR and MAPK pathways involve in endocrine resistance and breast cancer stem cell character. Moreover, it also reveals the extensive and complex role about BCSCs and BCSC-related pathways for endocrine resistance. BCSCs can depend on the GFR signaling pathway to survive, and escape from estrogen deprivation based on their ER$^-$ status [29, 33, 34]. Eventually, BCSCs will become the root cause of refractory resistance and escort breast cancers toward “permanent survival”. The combinations of targeted therapies focused on IGF-1R [35], HER2 [36, 37], or epidermal growth factor receptor [38–40] and endocrine therapy, even dual-targeting therapies plus endocrine therapy, have been shown not to reverse endocrine resistance or significantly enhance the effects of endocrine therapy. It has been suggested that breast cancers can still maintain endocrine resistance through the synergy of other pathways after inhibiting a small portion of these pathways. In conclusion, the process of endocrine resistance in breast carcinomas is the synergy of multiple mechanism. A new solution needs to be conceived.

The Hippo pathway

The Hippo pathway is also called the Salvador/Warts/Hippo pathway, and can precisely control the number of cells and stop organism growth in a timely manner during the development of mammals.

Hippo pathway and its dysregulation

When the phosphorylation cascades of the Hippo pathway become blocked, these cells will differentiate abnormally and gradually develop into malignancies [70]. Then, inhibited or disabled Hippo phosphorylation cascades of Hippo pathway will further facilitate the invasion and migration of tumor cells [71, 72]. The mechanism of the canonical Hippo pathway and its dysregulation is described in Fig. 2. The activated Hippo pathway
participates in the reasonable regulation of apoptosis and cell growth, when transcriptional coactivator with PDZ-binding motif (TAZ), and homologous component the yes-associated protein (YAP) are inactivated via their phosphorylation cascade. A variety of upstream signals activate mammalian sterile20-like (MST) kinases, and then MST kinases phosphorylate large tumor suppressor (LATS) kinases [73]. The activated LATS1/2 kinases can change the status of the phosphorylation and distribution of YAP/TAZ [74] resulting in the arrest of the cell cycle [75, 76]. LATS [77] and MST [73] are considered to have antitumor effects, and play negative roles in the regulation of TAZ and YAP. The entry of phosphorylated YAP/TAZ into the nucleus is restricted, and YAP/TAZ will be degraded after transferring into the cytoplasm from the nucleus, which can turn off antiapoptotic gene transcriptions and the cell cycle progression [78]. Conversely, when the Hippo pathway is dysregulated, the expression of downstream target genes of the Hippo pathway will promote cell proliferation and inhibit apoptosis genes, facilitating malignancies [79]. Dysregulation of the Hippo pathway showed results in excessive activation [80] or increased nuclear localization of YAP/TAZ by relatively decreasing YAP/TAZ phosphorylation [81], inhibiting LATS [82] and MST [83, 84]. Therefore, activated YAP and homologous TAZ are the core regulators of this pathway, since both of them exert oncogenic roles [85, 86] in the presence of a dysregulated Hippo pathway. Moreover, the low expression of MST and LATS will lead to the loss of control of YAP and TAZ [87]. Beyond this, additional non-canonical roles of the Hippo pathway in breast cancer have gradually emerged in recent years.

Fig. 3 Preliminary illustration of non-canonical roles between the Hippo pathway and ER signaling in breast cancer. Feedback was formed between YAP/TAZ and ER. YAP and TEAD function as co-regulators of ER signaling to facilitate gene transcription of ER signaling genes.
Breast cancer stem cell character suppression by the Hippo pathway

It has been confirmed that TAZ, YAP, LATS, and TEA domain family members (TEAD) are involved in the regulation of BCSCs. Cordenonsi et al. [88] first linked the Hippo pathway to the concept of BCSC proliferation. Since then, studies have confirmed that BCSCs can be facilitated by TAZ [89–93], YAP [94–97], as a homology of TAZ, the same as LATS [98] or TEAD [99], can also regulate BCSCs. Liu et al. [90] showed the restoration of sensitivity to tamoxifen and suppressed BCSCs by inhibiting TAZ expression. Moreover, dysregulation of the Hippo pathway is one of the prerequisites for the progress of an epithelial-mesenchymal transition (EMT) [100], which enables tumor to maintain the stem cell character [88]. MiR-520b activates the Hippo/YAP signaling pathways by targeting LATS, increasing the mRNA level of BCSC markers, such as CD133, CD44, and ALDH1, and the EMT marker N-cadherin in breast cancer [94]. Therefore, reactivating the Hippo pathway can effectively combat endocrine resistance and the expression of several oncogenes facilitated by BCSC transition.

The cross talk between the Hippo pathway and multiple pathways involved in endocrine resistance

Breast cancer can rely on ER signaling to promote cell proliferation, which is different from other tumors. The Hippo pathway is indeed associated with almost all pathways related to endocrine resistance, including ER signaling. Researchers have found partial cross talk between the Hippo pathway and ER signaling. Recent studies have found that targeting and activating the Hippo pathway...
can negatively regulate BCSCs and overcome endocrine resistance. Moreover, it also seems to be involved in the integration of GFR signaling pathways and Hippo pathway. This indicates that the Hippo pathway may make an unexpected contribution to endocrine therapy in ER+ breast cancers.

**The correlation between the Hippo pathway and the ER signaling pathway**

Preliminary non-canonical roles between the Hippo pathway and ER signaling in breast cancer is described in Fig. 3. On the one hand, the non-canonical roles of the components in Hippo pathway play a vital role in the management of ER signaling. YAP1 and TEAD4, co-regulators of ERα on enhancers, are augmented upon estrogen stimulation and transduction of target genes of ER signaling [101]. In addition, the expression of ERα was shown to directly be increased by YAP1 or indirectly mediated by the fork head box protein M1 (FOXM1) in the absence of the tumor suppressor Ras-association domain family 1 [102]. YAP/TAZ have also been shown to mediate the process of target gene induction by GPER [103]. On the other hand, ER can also affect the Hippo pathway. A study on mouse morula and trophoblast stem cells found that the nuclear localization of YAP was indeed regulated by ERα [104]. Moreover, the invasion and migration of TNBC were inhibited when the nuclear localization of YAP was inhibited, while sometimes the same situation did not appear in ER+ breast cancer, which may have been related to the compensatory increase in the nuclear localization of YAP mediated by ER [105]. The status of ER can also affect the interaction between cellular retinoic acid binding protein 2 (CRABP2) and LATS to regulate the Hippo pathway and modulate sensitivity to endocrine therapy [106]. Moreover, GPER facilitates the progression of breast cancer by activating YAP/TAZ [103]. A study of tumor breast (226 samples) and normal (40 samples) from microarray samples found that the level of YAP expression was evidently downregulated in invasive cancer samples compared to normal tissues samples, and decreased expression of YAP was remarkably associated with ER− status [107]. This suggested that invasive breast cancer cells with reduced expression of YAP were more likely to be ER− and may have an lower threshold for becoming resistant to endocrine therapy. Feedback regulation of hormone receptors on the Hippo pathway in turn was weakened by the down-regulation of ERα expression, and also was decreased by downward fluctuation of YAP. It may be the explanation for the lower YAP levels in invasive breast cancer are relative to normal breast tissue. The non-canonical Hippo pathway can in turn act on ER receptors to antagonize endocrine therapy, which can eventually leads to driving forces for tumor growth conversion to GFR signaling after estrogen-deprivation therapy. The regulation of the Hippo pathway for breast cancers dependent on different ER status and the different stage of endocrine resistance may be different [98, 106]. Thus, the study of the Hippo pathway in breast cancer cannot be generalized like other hormone-independent tumors.

**Antagonism of the Hippo pathway for endocrine resistance in ER+ breast cancer**

Studies in the MCF7 cell line (ER-positive breast cancer) have confirmed that correcting dysregulation of the Hippo pathway is a feasible scheme to inhibit breast cancer and overcome acquired drug resistance. The roles of the Hippo pathway in ER+ breast carcinoma are described in Fig. 4. In summary, YAP and TAZ surely are carcinogenic. Although the regulation of Hippo has been rarely studied in endocrine-resistant cells, the great prospect for modulation of the Hippo pathway has become an important research object. Zhou et al. [103] found that GPER’s role in inducing endocrine resistance could be regulated by the Hippo pathway and found that YAP was overexpressed in GPERhi breast cells. GPER activated YAP/TAZ, suggesting that blockage of GPER by knockdown of YAP/TAZ was a great strategy for overcoming tamoxifen resistance in GPERhi breast cancers. Moreover, Zheng et al. [108] found that the YAP-glycolysis axis was also a target for overcoming tamoxifen resistance, based on the fact that the Hippo pathway was downstream of GPER. Li et al. [109] confirmed that downregulated YAP phosphorylation and upregulated YAP nuclear translocation directly resulted in tamoxifen resistance, which was reversed by YAP silencing.

**Cross talk between the Hippo pathway and BCSC-related pathways**

The Hippo pathway plays a “co-correlation point” role in several networks of BCSC-related pathways, including Notch, Wnt, EGFR, PI3K/Akt, MAPK/ERK1, Hh/GLI2,TGF-β pathway. Clara et al. [85] first proposed that the Hippo pathway may be the “hub” of cancer stem cell related pathways. The cross talk between Hippo and BCSC-related pathways except ER signaling has been shown as described in Fig. 5. Hippo pathway does cross-talk these seven pathways, and there forms “bridges” between Hippo, Wnt, EGFR and PI3K/Akt pathways through WBP2. And these “bridges” do enable GFR signaling pathways and BCSC-related pathways to form crosstalk. Extensive integration and local interlinkages reveal the advantages of Hippo pathway in regulation of drug resistance through breast cancer stem cell character. In addition, Hippo, TGF-β, Hh, MAPK, Wnt, PI3K/Akt, Notch, EGFR, and ER signaling were all associated with
the EMT process. It has been further revealed that these pathways facilitate the synergistic regulation of breast cancer and can cause endocrine resistance in breast cancer. It is of no doubt, then, that the dysregulation of the Hippo pathway indeed facilitated the progression of breast cancer, and exert intricate cross talk on BCSC-related pathways. BCSCs are the key to maintaining refractory survival and drug resistance for tumor cells, which is based on the coregulation of these pathways. Therefore, the “co-correlation point” role of the Hippo pathway in BCSC-related pathways may highlight a new solution for overcoming endocrine resistance.

The interrelation between the Hippo pathway, GFR, and the Cyclin-dependent kinase 4 and 6 pathways

The rest of GFR signaling pathways and Cyclin-dependent kinase 4 and 6 pathways involved in endocrine resistance also exert cross talk on the Hippo pathway. With regards to patients with luminal B subtypes, samples with low TAZ resulted in higher pathological complete response rates after trastuzumab-based neoadjuvant therapy, suggesting that HER2 linked with TAZ expression in a consistent manner [126]. YAP/TAZ dephosphorylation and overexpression increased in trastuzumab-resistant breast cancer cells, suggesting that the dysregulated Hippo pathway further facilitated cancer cells in coordination with HER2 [127]. Inhibiting YAP and TAZ could eliminate Lapatinib resistance, suggesting that dual target therapy for HER2 and the Hippo pathway had good prospects [128]. The Hippo pathway mediated FGFR signaling, the MAPK pathway, and PI3K signaling during tumorigenesis, and YAP/TAZ were shown to be possible therapeutic targets in RTK-driven cancers [129]. The phosphorylation of MST1 depended on the activity of fibroblast growth factor receptor 4 kinase. Moreover, short-term suppression or knockdown of FGFR4 led to increased activation of MST1/2 [130]. The IGF-1R/ YAP axis has been shown to be involved in the growth of TNBC [131]. Dysregulation of the Hippo pathway also can increase resistance to CDK4/6 inhibitors through accumulation of TAZ and YAP transcription factors on the promoter of Cyclin-dependent kinase 6 [5]. These studies further demonstrated the great potential of the Hippo pathway for remediing breast cancer.

Integration of Hippo pathway in complex mechanism of endocrine resistance

These roles of Hippo pathway in the integration of ER signaling are unique to breast cancers. The regulation of Hippo pathway on cancer stem cells is also affirmed, including BCSCs. Hippo pathway can not only combat BCSCs, but also can integrate these multiple pathways involved in endocrine resistance, including GFR (PI3K/Akt/mTOR, EGFR, MAPK, HER2, IGF-1R and FGFR), BCSC-related pathways (Wnt, PI3K/Akt/mTOR, Hh, EGFR, Notch, MAPK, TGF-β, ER), and CDK4/6 pathway. The “co-correlation point” role of Hippo pathway in the multiple mechanism of endocrine resistance as described in Fig. 6. To sum up, utilizing the Hippo pathway as a therapeutic target for combating endocrine-resistant breast cancer may be a promising approach.

Agents and miRNAs for research proposals focusing on the Hippo pathway

In the process of endocrine therapy, the main driving forces for tumor growth were related to GFR signaling and even BCSC-related pathways. A dysregulated Hippo pathway did exert cross talk on these endocrine resistance-related pathways. A new therapeutic scheme that could be proposed to combat the “co-correlation point” of these pathways would focus on targeting the Hippo pathway. The combination of endocrine therapy and targeted therapy focusing on the Hippo pathway is expected to significantly improve the prognosis of patients with ER+ breast cancers. There are many agents that can target the Hippo pathway, including

(See figure on next page.)

**Fig. 5** Illustration of the crosstalk of the Hippo pathway and BCSC-related pathways. Linc-OIP5 promotes transcription via forming a positive feedback circuit between YAP and Notch signaling [115]. IMF3 indirectly promotes Wnt5B via miR145-5p and facilitates TAZ-driven gene expression [116]. YAP and TAZ can promote the Wnt/β-catenin/TCF axis and induce target genes by interaction with β-catenin, while WBP2 integrates the Hippo, Wnt, and PI3K pathway [117–119]. Mir-613 inhibits EGFR via directly inhibiting WBP2 and positive correlation of EGFR and WBP2 is confirmed, while EGFR promotes WBP2 phosphorylation, contributing to integration of the Wnt/β-catenin and Hippo pathways [118, 119]. YAP/TAZ mediate the synergistic function and oncogene expression induced by the PI3K and dysregulated Hippo pathways [120]. The MAPK/ERK1 pathway negatively regulates breast cancer proliferation by inhibiting YAP/TEAD [121]. YAP induces gene transcription and promotes glycolysis by wiring up the Hh/Gli2 axis [108]. The SnoN oncoprotein exerts negative feedback regulation on TGF-β signaling, while promoting TAZ signaling and enhancing gene transcription in breast cancers [122]. Zyxin forms a ternary complex with LATS and Siah, which facilitates the degradation of LATS, activation of YAP and subsequently cell proliferation [123]. The tumor suppressor Merlin can inhibit YAZ/TAZ and maintain Smad7 stability, suppressing the adaptive glycolysis facilitated by the interaction between YAP/TAZ and Smads [124]. Ski inhibits breast cancer by suppressing TAZ in a LATS-dependent manner or in a LATS-independent manner, in which NCoR1 is recruited by Ski and suppresses TAZ by binding to the TEAD-TAZ complex [125].
Pevonedistat, Verteporfin, stains, and Metformin [85, 132]. Statins and Metformin are commonly used to regulate metabolism of lipids and glucoses. In recent years, there are clinical trials targeting the Hippo pathway, although no available results. Clinical trials are designed for targeting the Hippo pathway as illustrated in Table 3. Clinical trials of combination of endocrine therapy and agents targeting Hippo pathway for reference as illustrated in Table 4. Moreover, the regulation of miRNAs is also an alternative tool. MiRNAs are related to the Hippo pathway in breast cancers, as illustrated in Table 5 and Fig. 7. Partial miRNAs can also be involved in the regulation of EMT [94, 133–135] and the maintenance of stem cell character in breast cancer [94, 134, 135]. MiR-125a-5p [136], the miR-200 family [137], miR-375 [138], and miR-181b [139], have all been recommended as therapeutic agents, since all of them can regulate endocrine resistance and were confirmed to be related to the Hippo pathway in other tumors. Upregulation of miR-125a-5p in tamoxifen resistant MCF7 cells may inhibit the growth of BCSCs by suppression of TAZ, which is an effective promoter of BCSCs. It is expected that the results of preclinical and clinical data will confirm its role in the future.

### Conclusion and prospects
Targeting the Hippo pathway has been researched in a variety of tumors and has been shown to have remarkable results. The combination of targeted therapy for the Hippo pathway and chemotherapy or other targeted

**Table 3** Designed clinical trials of agents targeting the Hippo pathway

| Agents | Mode of action | Study phase | Outcome | Study Title | NCT number |
|--------|----------------|-------------|---------|-------------|------------|
| Zoledronate, Atorvastatin | Inhibition of YAP/TAZ | Phase 2 | No results available | Neoadjuvant Zoledronate and Atorvastatin in TNBC | NCT03358017 |
| Atorvastatin | Inhibits TAZ | Phase 2 | No results available | Targeting the Hippo transducer TAZ in breast cancer with Statins | NCT 02416427 |
| Zoledronate | Inhibits YAP/TAZ | Phase 2 | No results available | Pre-operative zoledronate in TNBC | NCT 02347163 |

**Table 4** Clinical trials of endocrine therapy combined with agents targeting Hippo pathway for reference

| Agents | Endocrine therapy | Study phase | Outcome | NCT number | Possible mechanisms |
|--------|-------------------|-------------|---------|------------|---------------------|
| Atorvastatin | Letrozole, Fulvestrant | Phase 2 | No results available | NCT02958852 | Stains inhibits YAP/TAZ nuclear localization, and suppressed the self-renewal capability of cancer stem cells via opposing nuclear TAZ activity [140] |
| Metformin, Simvastatin | Fulvestrant | Phase 2 | No results available | NCT03192293 |
| Metformin | Toremifene | Phase 2 | No results available | NCT02506790 |
| Metformin | Fulvestrant | Phase 2 | No results available | NCT04300790 |
| Metformin | Everolimus, Exemestane | Phase 2 | The clinical benefit rate was 54.5% | NCT01627067 | Metformin inhibits YAP nuclear localization [141] |
therapies has also achieved initial results in breast cancers. Although its dysregulation can promote the occurrence and progression of tumors, reasonable regulation of this pathway can effectively inhibit tumors and combat endocrine resistance. However, the Hippo pathway is powerful, diverse, and complex. Breast cancers differ from other tumors, in that the former is derived from more of the non-canonical roles of the Hippo pathway via hormone receptors. More studies are needed to verify the feasibility and risk of regulation of the Hippo pathway in endocrine-resistant breast cancer. Moreover, our laboratory has shown that aromatase inhibitors such as Formestane can rely on ER-independent but androgen receptor-dependent roles to suppress ER+ breast cancer, suggesting that aromatase inhibitors may be highly recommended as promising agents combined with targeting the Hippo pathway to significantly overcome endocrine resistance stimulated by estrogen-deprivation therapy in postmenopausal women [157]. Targeting the Hippo pathway will create promising new tools in the fight against endocrine-resistant breast cancer.

| MiRNAs               | Tumor suppressor (−)/tumor promotor (+) | Cell lines                       | Targets          | Mechanisms of regulation |
|----------------------|----------------------------------------|----------------------------------|------------------|--------------------------|
| MiR-326 [142]        | −                                      | MCF-7, MDA-MB-468                | TAZ              | Circular RNA 0000511 can eliminate the anti-tumor effect of miR-326 by upregulating TAZ |
| MiR-146b [143]       | −                                      | MCF-7                            | p-YAP            | The process of MUC19 reducing YAP phosphorylation is inhibited by miR-146b |
| MiR-199a-3p [133]    | −                                      | MDA-MB-231                        | LATS1, YAP1      | miR-199a-3p suppresses YAP1 and upregulates LATS1 |
| MiR-574-5p [135]     | −                                      | MDA-MB-231, T47D                  | TAZ              | miR-574-5p targets Sox2 to suppress TAZ |
| MiR-1297 [144]       | −                                      | MDA-MB-231, MDA-MB-468           | TAZ              | miR-1297 inhibits TAZ |
| MiR-125a-5p [145, 146]| −                                      | MDA-MB-468, Bt549, tamoxifen resistant MCF7 | TAZ              | miR-125a-5p directly inhibits TAZ expression. Downregulation of CYTOR decreases protein and mRNA levels of TAZ in tamoxifen resistant MCF7 cells, which is rescued by miR-125a-5p suppression |
| MiR-515-5p [147]     | +                                      | MDA-MB-231, MDA-MB-453           | YAP, TAZ, p-TAZ  | Knockdown LINC00673 reduces the level of YAP/TAZ and increases p-YAP through miR-515-5p inactivation |
| MiR-591 [148]        | −                                      | MCF-7, SKBR3                      | YAP, LAT5        | miR-591 inhibits YAP and upregulates LAT5 |
| MiR-520b [94]        | +                                      | MCF-7, MDA-MB-231                | LAT52, p-YAP, YAP| miR-520b promotes migration activity and stemness of breast cancer, which can be abolished by overexpression of LAT52. miR-520b upregulates nuclear YAP and inhibits LAT52 as well as p-YAP |
| MiR-372 [149]        | +                                      | MCF-7, MDA-MB-231                | LAT52            | miR-372 inhibits LAT52 |
| MiR-18a [150]        | −                                      | Trastuzumab-resistant SKBR-3      | YAP1             | miR-18a directly inhibits YAP1 |
| MiR-424 [151]        | −                                      | MDA-MB-231, HCC-1937             | YAP              | miR-424 inhibits YAP |
| MiR-205 [134]        | −                                      | SUM159                           | TAZ              | miR-205 inhibits TAZ, which is involved in the mammospheres formation and BCSC renewal |
| MiR-135b [152]       | +                                      | MDA-MB-231, MCF-7, 293 T          | LAT52,           | miR-135b inhibits LAT52 |
| MiR-506 [153]        | −                                      | MDA-MB-231                        | LAT52            | miR-506 inhibits YAP |
| MiR-31 [154]         | +                                      | MDA-MB-231                        | LAT52            | miR-31 inhibits LAT52 |
| MiR-93 [155]         | +                                      | MT-1                             | LAT52            | miR-93 inhibits LAT52 |

**Table 5** MiRNAs that regulate the Hippo pathway in breast cancer

| MiRNAs               | Tumor suppressor (−)/tumor promotor (+) | Cell lines                       | Targets          | Mechanisms of regulation |
|----------------------|----------------------------------------|----------------------------------|------------------|--------------------------|
| MiR-372 [149]        | +                                      | MCF-7, MDA-MB-231                | LAT52            | miR-372 inhibits LAT52 |
| MiR-18a [150]        | −                                      | Trastuzumab-resistant SKBR-3      | YAP1             | miR-18a directly inhibits YAP1 |
| MiR-424 [151]        | −                                      | MDA-MB-231, HCC-1937             | YAP              | miR-424 inhibits YAP |
| MiR-205 [134]        | −                                      | SUM159                           | TAZ              | miR-205 inhibits TAZ, which is involved in the mammospheres formation and BCSC renewal |
| MiR-135b [152]       | +                                      | MDA-MB-231, MCF-7, 293 T          | LAT52,           | miR-135b inhibits LAT52 |
| MiR-506 [153]        | −                                      | MDA-MB-231                        | LAT52            | miR-506 inhibits YAP |
| MiR-31 [154]         | +                                      | MDA-MB-231                        | LAT52            | miR-31 inhibits LAT52 |
| MiR-93 [155]         | +                                      | MT-1                             | LAT52            | miR-93 inhibits LAT52 |
Abbreviations
TNBC: Triple negative breast cancer; FOXM1: Fork head box protein M1; BCSCs: Breast cancer stem cells; USP9X: Ubiquitin-specific protease 9X; ER+: Estrogen receptor-positive; CDKs: Cyclin-dependent kinases; mTOR: Mammalian target of rapamycin; WBP2: WW domain-binding protein 2; E2: Estradiol, PI3K: Phosphoinositide 3-kinase; ER: Estrogen receptor; GFR: Growth factor receptor; PFS: Progression-free survival; GPER: G protein-coupled estrogen receptor; ER−: Estrogen receptor negative; Hh: Hedgehog; TGF-β: Transforming growth factor β; IMP3: Insulin-like growth factor-2 mRNA-binding protein 3; E2F: Estrogen response element; MAPK: Mitogen-activated protein kinase; CRABP2: Cellular retinoic acid binding protein 2; HER2: Human epidermal growth factor receptor 2; FGFR: Fibroblast growth factor receptor 1; NCoR1: Nuclear transcriptional corepressor N-CoR1; BCAR4: Breast cancer anti-estrogen resistance 4; IGFBP-1: Insulin-like growth factor 1 receptor; YAP: Yes-associated protein; EPI: Epinephrine; NE: Norepinephrine; ceRNA: Competing endogenous RNA; ERK1: Extracellular signal-related kinases 1.

Acknowledgements
We thank all the members of Sichuan Provincial Center for Gynaecology and Breast Disease for the technical assistance and research support.

Authors’ contributions
ATT was in charge of conception, design, investigation, data analyses, funding acquisition, editing, review and formal analysis of the findings being published. JC wrote original draft and drew figures. JC gave assistance to investigation, data analyses, translation. RLW was responsible for supervising the process. QQL, ZHR, YLW and LZ gave assistance to translation and language. All authors read and approved the final manuscript.

Funding
This research was funded by the Fund for High-level Talents in Luzhou City (No. 02-00040055).
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