REVIEW PAPER

DOI: https://doi.org/10.20883/medical.e25

TAZ oncogene as a prognostic factor in breast cancer

Aleksandra Glapa[1], Aleksandra Nijak[2]

[1] Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, Poland
[2] Department of Cancer Immunology, Poznan University of Medical Sciences, Poland

ABSTRACT

Breast cancer is the most frequently diagnosed cancer in females and one of the main causes of cancer related deaths. Breast cancer in the metastatic stage is related with poor prognosis. Metastasis is the process whereby cancer cells travel to and colonize distant sites through the lymphatic system or bloodstream, which usually indicates a poor prognosis. The metastatic cascade involves several molecular and cellular interactions and different signaling pathaways. Recently the Hippo signaling has emerged as an important regulatory pathway in cancer. The Hippo target protein TAZ has been reported as a novel oncogene that may have important role in the development of breast cancer. Its overexpression promotes cancer stem cell formation and epithelial–mesenchymal transition in many human cancers. In breast TAZ seems to play a critical developmental role and in breast cancer is one of the factors involved in therapeutic resistance and clinical relapse. Herein, we review the biological functions of TAZ and summarize the current knowledge and opportunities for therapeutic intervention in this field.

Keywords: breast cancer prognosis, cancer stem cells, Hippo pathway, targeted therapy.

Introduction

Breast cancer is one of the most common cancers in women and a cause of around a half million deaths annually worldwide (World Cancer Report 2014. International Agency for Research on Cancer, World Health Organization. 2014.). Numerous studies show that the pathogenesis of breast cancer is highly related with a small population of cells with stem cell characteristics which are named cancer stem cells (CSC). One of the important regulators of CSC phenotype is the Hippo tumor suppressor signaling pathway.

Hippo pathway is a main downstream effector regulating cell proliferation, tumor formation, apoptosis and organ size [2]. Highly conserved in its structure, the pathway was originally described in Drosophila melanogaster as an organ size regulator. It consists of a cascade of kinases, MST and LATS in mammals, that phosphorylate the effector proteins YAP and TAZ, thereby controlling their nucleo-cytoplasmic localization and functions. MST1/2 phosphorylate and activate the kinases LATS1/2, which in turn phosphorylate YAP and TAZ, leading to their cytoplasmic retention [3]. Inactivation of the MST and LATS kinases results in nuclear accumulation of oncoproteins YAP and TAZ and subsequent activation of target genes, many of them involved in cell proliferation and epithelial-to-mesenchymal transition (EMT).

TAZ (transcriptional co-activator with PDZ-binding motif) is a component of the pathway, which structurally shares 50% sequence identity with its paralog –YAP. TAZ contains one WW domain, which allows it to bind other partners that exhibit proline-rich modules named PY motifs [4]. In the cell nucleus TAZ binds with the primary partners which are TEA domain (TEAD) transcription factors. TAZ function as transcriptional co-activator for them, therefore overexpression of TAZ induces

cell transformation and tumor-forming ability in mammary epithelial cells [5]. The deactivation of the Hippo pathway, which leads to upregulation of YAP and TAZ is frequently observed in many human cancers.

TAZ is reported to confer cancer stem cell-related traits on breast cancer cells and a novel oncogene that may have important roles in the development of breast cancer.

Herein, we review of the Hippo pathway in human, and discuss the biological functions of TAZ and summarize the current knowledge and opportunities for therapeutic intervention in this field.

The Hippo pathway

Numerous studies show that the Hippo pathway plays a key role in tumorigenesis. Its deregulation is frequently observed in many human cancers. Deactivation of Hippo pathway leads to YAP and TAZ translocation into nucleus which in turn promotes transcription of downstream genes by forming complexes with transcription factors. Conversely, Hippo pathway activation, cause YAP and TAZ sequestration in the cytoplasm and further degradation.

The Hippo pathway also plays an important role in normal mammary gland development. TAZ is reported to regulate the number and complexity of branches within mammary gland and determine the fate of basal and luminal cells in mammary glands [6, 7]. The Hippo pathway was reported to be highly transcriptionally deregulated but only in case of basal-like subtype of breast cancer.

TAZ in human cancer

A range of cancers displays high levels of TAZ or YAP expression such as carcinomas of the lung, thyroid, ovarian, colorectal, prostate, pancreas, esophagus or liver [8–10]. This high level of expression has been associated with shorter patient overall survival [11–13].

In non-small cell lung cancer TAZ protein was reported to be expressed in 66.8% cases (that is 121/181), which also significantly correlated with poorer differentiation and short survival [14]. In gastric cancer samples, Yue et al reported TAZ positive expression in 77.4% (113 out of 146) and especially higher expressed in signet ring cell carcinoma [15]. The level of TAZ mRNA could also be a prognostic marker in colon cancer progression [11]. This data indicates that TAZ may become a worthy target for therapeutic intervention in future.

TAZ in breast cancer

TAZ is overexpressed in ~21.4% of breast cancer samples, particularly these fulfilling the histopathological criteria of poor differentiation or high grade [5]. Cordenonsi et al.. has previously reported that, CSCs are indeed enriched in high-grade breast cancers (i.e., poorly differentiated tumors classified as G3 by histopathological criteria) when compared to well-differentiated, low-grade (G1) tumors [16]. That fact suggests that TAZ plays a critical role in the migration, invasion, and tumorigenesis of breast cancer cells.

Chan et al. observed that f2- to 3-fold gain of function (by overexpression) in MCF10A cells increased the migratory and invasive properties such as loss of cell adhesion and increased cell mobility of the cells. Furthermore, the overexpression resulted in morphologic change from an epithelial to a fibroblast like appearance indicating that TAZ may take part in regulation of EMT/MET events in breast epithelial cells. The strict mechanism of this action is vague as the expression level of E-cadherin in MCF10A and MCF7 cells is not significantly altered by either overexpression or knockdown of TAZ. In turn, the knockdown of TAZ using short hairpin RNA retard anchorage-independent growth in soft agar in MCF7, although it is not sufficient to enable MCF10A cells to grow into sizeable colonies in this assay and tumorigenesis in nude mice [5].

Cordenonsi et al. indicate that loss of cell-polarity determinant Scribble is one of the responsible factors to induce EMT in breast epithelial cells. TAZ forms a complex with Scribble, and its loss disrupts the inhibitory association of TAZ with MST and LATS. This findings reveals that cell polarity may control of Hippo pathway [17]. Lei et al. reported that constant TAZ expression stimulates cell proliferation with an increase in the S-phase cell population [2]. Furthermore TAZ negatively correlates with disease-free survival in patients with breast cancer [18].

The tumorigenic properties of TAZ may be due to WW and PDZ-binding domains, which play a crucial role in self-renewal of mammary tissue. WW domains of TAZ act through interaction with PPXY motifs of some transcriptional factors. For instance the Runx transcription factors (Runx1, Runx2 and Runx3 that are involved in carcinogenesis and cancer metastasis. Both YAP and TAZ can potentiate Runx activity through WW-PPXY interaction [19]. Moreover, transduction of MCF10A cells with the WW domain mutation results in significantly fewer colonies in soft agar assay in comparison to the wild-type TAZ [20].

The highly conserved PDZ-binding motif localized in the C-terminus of TAZ also confers mammary tumour formation potential. It localizes TAZ into discrete nuclear foci and is essential for TAZ-stimulated gene transcription. Loss of the PDZ-binding motif is reported to abrogate tumour formation in vivo.

The main targets of the YAP and TAZ belong to the TEAD protein family (TEAD1-4) and they function as regulators of cell contact inhibition, EMT, oncogenic transformation and apoptosis inhibition. Li et al. demonstrated that silencing of TEAD1, TEAD3 and TEAD4 by RNAi as well as disruption of TAZ-TEAD binding resulted in completely abrogation of CSC-like traits driven by TAZ [21]. TAZ has also been reported to interact through the WW domain with the PPXY motif of the Kruppel-like factor 5 (KLF5). By this means TAZ protects KLF5 from WWP1-mediated ubiquitination and further degradation, which in turn leads to breast cell proliferation and tumorigenesis [22, p. 5]

Relation to cancer stem cells

The Hippo transducer TAZ confers CSC-related traits on breast cancer cells such as the ability to drive tumorigenesis and contribute to maligancy, therapeutic resistance and clinical relapse. The expression level of TAZ is higher in breast CSCs than that in differentiated breast cancer cells. Expression of cell surface markers is of some assistance in distinguishing the tumorigenic from the nontumorigenic cancer cells. In breast cancer the $CD44^{+}CD24^{-}$ phenotype confers the tumorigenic properties. Serial passaging of this tumorigenic subpopulation generated new tumours containing additional $CD44^{+}CD24^{-/low}Lineage^{-}$ tumorigenic cells as well as populations of nontumorigenic cells present in the initial tumor. TAZ has been determined to be required for the maintenance of the $CD44^{high}/CD24^{low}$ antigen phenotype [5, 23, 24]. Moreover, the $CD44^{high}/CD24^{low}$ subpopulation characterized by a lower in vitro proliferation rate compared to parental cells and resistance to chemotherapy [24].

TAZ induces chemoresistance

Numerous studies show the association between TAZ and chemoresistance of breast cancer [25, 26]. For instance, elevated TAZ levels lead to resistance to the first- line chemotherapeutic drug in breast cancer- Taxol [26]. TAZ contributes to Taxol resistance by inducing the transcription of TAZ targets Cyr61 and CTGF. Lai et al. has knockdowned genes Cyr61 and CTGF by short hairpin RNA in MDA-MB231 in breast cancer cells, what reversed Taxol resistance in these cells. Activation of the Cyr61/CTGF promoters and induction of Taxol resistance was driven by the interaction of TAZ with the TEAD family of transcription factors . Hence the TAZ-TEAD-Cyr61/CTGF signalling pathway is an important modifier and a therapeutic target of the Taxol response in breast cancer cells.

TAZ as prognostic factor

Recently TAZ expression has been linked with HER-2 positivity and the pathological complete response [27]. Patients with low TAZ tumors exhibited pathological complete response rate of 78.6% whereas patients with high TAZ tumors -57.6% ($p = 0.082$). Vici et al. suggest that the level of TAZ assessed by means of immunohistochemistry predicts pathological complete response in 61 patients receiving neoadjuvant chemotherapy and trastuzumab, with both molecular subtypes – Luminal B and HER2-positive.

TAZ as potent therapeutic target in cancer

TAZ has been proposed as a viable target in cancer therapy. The possible therapeutic strategies may include various strategies such as YAP/TAZ-TEAD interaction or upstream kinases [28–31]

Targeting the actin cytoskeleton with the F-actin destabilizers (Atrunculin A/B, Cytochalasin D, Blebbistatin) inhibits nuclear export of TAZ in Drosophila, therefore may be effective in control of tumour growth. [32, 33]. The Hippo pathway is also regulated by G-protein-coupled receptor (GPCR) signalling which can either activate or inhibit the Hippo-YAP pathway depending on the coupled G protein [34]. Ligands like 1-phosphophate (S1P), serum-borne lysophosphatidic acid (LPA), sphingosine thrombin and protease-activated receptor agonists signal through G12/13 coupled receptors, therefore inhibiting the Lats1/2 kinases, and activating TAZ [19]. Therefore, development of agonists mimicking LPA or S1P may be another therapeutic option [35–37]. Therefore, GPCRs are very prominent candidates for anti-cancer drug target [38].

It was also reported that TAZ may be activated by Wnt/βcatenin pathway. Active signalling leads β-catenin to detach from destruction complex and inhibit TAZ degradation, therefore maintaining integral β-catenin destruction complex abrogate TAZ. XAV939, G244-LM and G007-LK are tankyrase inhibitors restor-

ing the integrity of the complex enabling TAZ degradation [39].

Another possible strategy to inhibit nuclear localization and activation of TAZ is through metabolic cues [40]. The mevalonate–YAP/TAZ pathway is required for proliferation and self-renewal of breast cancer cells therefore it is crucial to develop mevalonate pathway inhibitors. Oncogenic cofactor mutant p53, which is the most frequently mutated in breast cancers, promotes transcription factor SREBP activity which in turn increases the levels of mevalonic acid. Mevalonate is a precursor for geranylgeranyl diphosphate (GGPP) which promotes membrane localization and activity of Rho GTPase, that leads to YAP/TAZ nuclear localization and activation. Inhibition of HMG-CoA reductase by statins or bisphosphonates blocks YAP/TAZ nuclear translocation and further transcription. Also, inhibition of geranylgeranylation of Gβγ and RhoA enhances phosphorylation of MST1/2 and LATS1, inhibits the activation of TAZ, and reduces the breast cancer cell migration [41].

Habbig et al. has determined that NPHP4, a known cilia-associated protein and an upstream regulator of TAZ, acts through interaction with LATS1, therefore inhibiting TAZ and YAP phosphorylation [42]. Similarly, NPHP9, competitively binds with TAZ, translocating TAZ into nucleus [43]. It has been shown that the knockdown of both of the proteins inhibits the breast cancer cell proliferation. These findings indicate new ideas for designing anti-YAP/TAZ drugs.

Recently Frangou et al. found that desatinib, a multi-target kinase inhibitor, may modulate TAZ-mediated pro-tumorigenic transcriptional programs [24]. In their study, Dasatinib inhibited the anchorage-independent growth of TAZ-M#1 cells in soft-agar assay and reduced self-renewal as measured by mammosphere formation. FACS analysis showed that TAZ-M#1 cells treated for 24 hours with Dasatinib were depleted of $CD44^{high}/CD24^{low}$ subpopulation, a phenotype associated with cancer stem cells. Conversely the $CD44^{high}/CD24^{high}$ breast cancer subpopulation remained viable. These results indicate that Dasatinib selectively eradicates the TAZ driven breast cancer initiating cells. Further research show that MDA-MB-231 cells treated with Dasatinib injected into SCID mice demonstrate a decreased tumor formation.

Conclusion

The development of breast and breast cancer is determined by multiple, genetic and environmental factors. The crosstalk between signalling pathways, as well as the strict upstream regulators and downstream target genes of the Hippo pathway has not been completely understood. Examination of the Hippo signalling seems to be important in designing more effective cancer therapeutics, especially targeting TAZ.

Acknowledgements

We gratefully acknowledge the writing assistance of Urszula Kazimierczak, PhD.

Conflict of interest statement

The authors declare that there is no conflict of interest in the authorship or publication of contribution.

Funding sources

There are no sources of funding to declare.

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Acceptance for editing: 2015-04-29
Acceptance for publication: 2015-05-28

Correspondence address:
Aleksandra Glapa
Department of Pediatric Gastroenterology and Metabolic Diseases
Poznan University of Medical Sciences
27/33 Szpitalna Str., 60-572 Poznań, Poland
phone: +48 691747051, fax: +48 618483362
email: 66345@student.ump.edu.pl