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Review Article

Regulation and function of the TAZ transcription co-activator

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Abstract: TAZ (WWTR1), identified as a 14-3-3 binding protein with a PDZ binding motif, is implicated in mesenchymal stem cell differentiation. TAZ has been shown to be negatively regulated by phosphorylation–dependent and phosphorylation-independent mechanisms. Coupled with ASPP2, PP1 dephosphorylates TAZ to activate TAZ. TEADs mediate TAZ function in promoting cell proliferation and epithelial-mesenchymal transition (EMT). TAZ senses different cellular signals such as cell density and the extracellular matrix stiffness. Significantly, TAZ is overexpressed in breast cancer samples and papillary thyroid carcinoma tissues. These results indicate that TAZ plays an important role in cancer development and presents a novel target for TAZ overexpressed cancer therapy.

Keywords: TAZ (WWTR1), 14-3-3 binding protein, PDZ binding motif, stem cell, epithelial-mesenchymal transition (EMT), signal transduction

Introduction

Organ size control is a fundamental question in biology. How the stem cells coordinate proliferation and differentiation to form specific tissue is a basic puzzle in development and organ regeneration. In the past decade, the discovery and studies of TAZ (transcriptional co-activator with PDZ-binding motif, TAZ) provide insights to address those fundamental questions. TAZ, also known as WWTR1 (WW-domain containing transcriptional regulator 1, WWTR1), was first identified as a 14-3-3 binding protein [1]. Sequence analysis revealed that TAZ shares homology with Yes-associated protein (YAP), previously identified as a binding partner of the SH3 domain of the Src-family kinase Yes [2]. Both TAZ and YAP contain WW domain, a 14-3-3 binding motif, a coiled-coiled motif in the transactivation domain and a PDZ-binding motif in the C-terminal (**Figure 1**). Those motifs and domains are critical for regulating TAZ function. As a transcriptional co-activator, TAZ has been shown to interact with and regulate multiple transcriptionalb factors, such as Runx2 (runt-related transcription factor 2 [3], PPAR perioxisome proliferator-activated receptor PPAR) [4], TBX5 (T-box transcription factor 5, TBX5) [5], TEADs (TEA domain family members, TEAD) [6-8], TTF-1 (thyroid TF1, TTF1) [9, 10], PAX3 (paired box homeotic gene 3, PAX3) [11]. Furthermore, studies of knockout mice [12-14] and clinical samples [15] have demonstrated that the significance of the TAZ function in organ development, stem cell differentiation and development of human cancer. Here, we summarize the current understanding of biochemical regulation mechanism of TAZ and the biological function of TAZ in development and differentiation, with the implication of TAZ's crucial role in human cancer development.

TAZ is phosphorylated and inhibited by the Hippo pathway

TAZ phosphorylation at Ser89 generates a 14-3-3 binding site and promotes TAZ-14-3-3 binding, thereby sequestrates TAZ in the cytoplasm [1]. Phosphorylation at Ser89 is a critical event for inhibiting TAZ transcriptional activity, but the kinase responsible for phosphorylating TAZ was unknown until a new emerging tumor suppres-

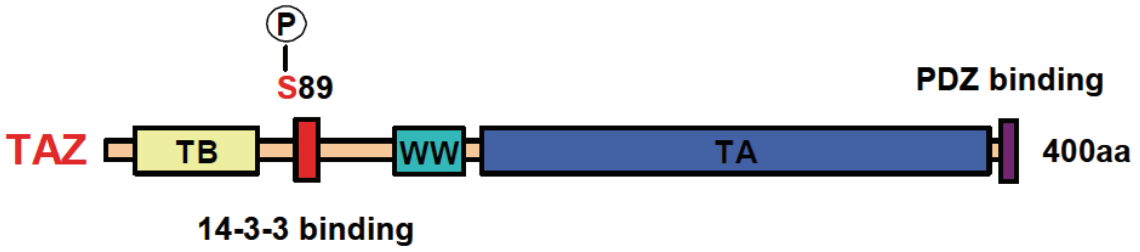

Figure 1 TAZ structure domain. TAZ contains WW domain, a 14-3-3 binding motif, a coiled-coiled motif in the transactivation domain and a PDZ-binding motif in the C-terminal. TB: Tead Binding Domain; TA: Transcriptional Activation Domain.

sor pathway, Hippo pathway, has been discovered and delineated in the genetic screen of tumor suppressor genes in *Drosophila*. The core components of Hippo pathway in *Drosophila* consist of two kinases, the ste-20 like kinase Hippo (Hpo) and the NDR family kinase Warts (Wts), and their binding partners, Salvador (Sav) and Mob-as-tumor-suppressor Mats, respectively. Hpo-Sav kinase complex phosphorylates and activates Wts-Mats kinase complex, followed by the activation of Wts kinase to phosphorylate its downstream target Yorkie (Yki), resulting in Yki inactivation [16].

Studies have demonstrated the Hippo pathway is conserved from *Drosophila* to Mammals. Components of the Hippo pathway are found in all eukaryotes and are highly conserved in multiple cellular organisms. For example, MST1/2 (macrophage stimulating 1 /2, MST1/2) and LATS1/2 (Large tumor suppressor homolog 1/2, LATS1/2) are human homologues of the *Drosophila* Hpo and Wts, respectively [17]. In mammals, Hippo pathway is composed of a kinase cascade that MST1/MST2, complexed with its regulatory subunit SAV1, phosphorylates and activates LATS1/2 in complex with its regulatory subunit MOB1, resulting in phosphorylation and inactivation YAP1 oncoprotein and WWTR1/TAZ (**Figure 2**) [17].

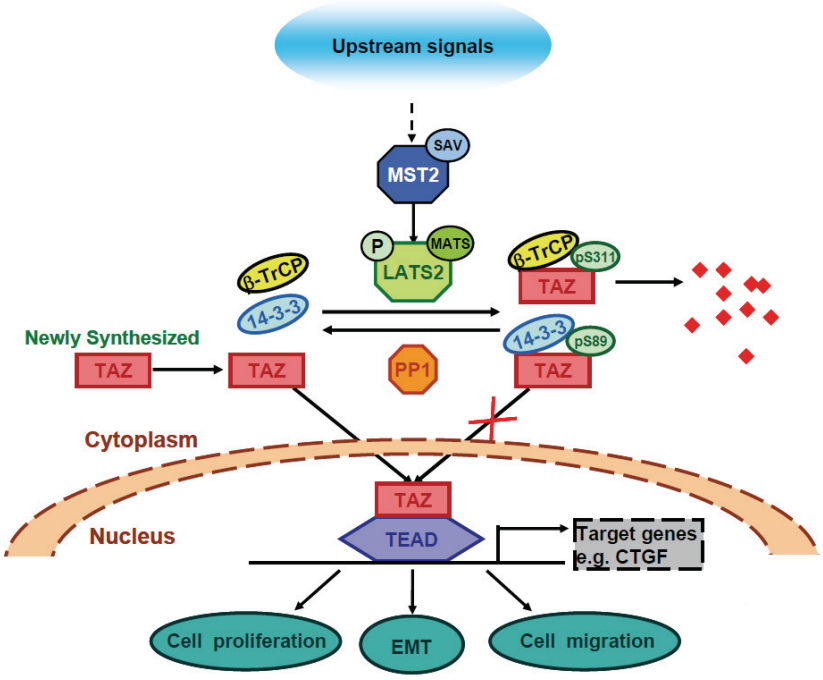

Figure 2 TAZ is regulated by LATS and PP1. TAZ is negatively and positively regulated by LATS kinase and PP1 phosphatase, respectively.

TAZ contains four consensus HxRxxS motifs. Besides Ser89, LATS kinase also phosphorylates TAZ at Ser 66, Ser117 and Ser311 [18]. LATS phosphorylates TAZ at Ser89 to enhance cytoplasmic retention of TAZ by increasing the interaction between TAZ and 14-3-3 [18]. This results in separation of TAZ with its transcription factors, therefore inhibition transcription of TAZ target genes. YAP, the homolog of TAZ, and Yki, the ortholog of YAP in *Drosophila*, are regulated in a similar manner [19]. Mutation of Ser89 in TAZ

renders TAZ resistant to negative regulation by Hippo pathway and constitutive activation as a transcriptional co-activator.

In addition to promoting TAZ translocation from nucleus to cytoplasm, LATS phosphorylates and destabilizes TAZ. TAZ possesses two DpSGX1-3pS β-TrCP phosphodegrons and phosphorylation of the C-terminal degron is mainly responsible for TAZ-β-TrCP interaction [20]. Phosphorylating Ser311 in TAZ by LATS confers a prime phosphorylation site for sequential phosphorylation Ser 314 by another kinase, CK1 (Casein Kinase 1, CK1). This cooperative phosphorylation recruits $SCF^{\beta\text{-}TrCP}$ E3 ligase and leads to polyubiquitynation and degradation of TAZ. This is consistent with not only TAZ retention in cytoplasm but also degradation in the normal mammary epithelial cells MCF10A at high density when the Hippo pathway is activated [20]. Mutation of the phosphorylation sites or the C-terminal degron itself all disrupted the interaction between TAZ and β-TrCP, therefore, stabilized TAZ to promote TAZ function. This mechanism is conserved in YAP, but not Yki, which doesn't contain a phosphodegron [21].

Other factors affecting LATS-TAZ complex formation

Given the important role of LATS in regulating TAZ function, TAZ can be regulated by other factors through affecting LATS-TAZ complex formation. For example, the ASPP1 is a member of the ASPP (ankyrin-repeat-containing, SH3-domain-containing, and proline-rich-region-containing protein, ASPP) family, containing four ankyrin repeats, an SH3 domain, and a proline rich region [22]. ASPP1 is shown to bind with and be phosphorylated by LATS2 [23]. Phosphorylated ASPP1 translocates into nucleus and promotes p53 to induce apoptosis [23]. Opposite to its tumor suppressor function of nuclear ASPP1, overexpression ASPP1 enhances TAZ/YAP nuclear localization and increases TAZ/YAP stability and TAZ/YAP target genes' expression [24]. This is due to ASPP1 impeding YAP/LATS2 interaction and decreasing the phosphorylation level of YAP [24], which may also be the same as ASPP1/TAZ. Cell contact inhibition has been shown to be a common stimulation of Hippo pathway and the tight junction components were recently identified to regulate Hippo pathway. Disruption tight junction by calcium depletion also impedes the interaction between TAZ and LATS1, thereby decreases Ser89 phosphorylation level [25]. But how tight junction regulates TAZ-LATS1 complex formation and which components of tight junction are involved in disrupting TAZ-LATS1 complex is unknown. Recently, cilia-associated protein NPHP4 (nephrocystin 4, NPHP4) has been reported to inhibit TAZ phosphorylation and activate its nuclear translocalization through the direct interaction with LATS1 [26].

PP1 coupled with ASPP2 to activate TAZ via dephosphorylation

Phosphorylation Ser89 and Ser311 in TAZ is an important event of TAZ regulation, the phosphatase responsible for dephosphorylating Ser 89 and Ser311 is also equivalently significant. PP1 (Protein Phosphatase 1, PP1) was first identified as TAZ interacting protein and then proven to be a *bona fide* phosphatase of TAZ [27]. Another TAZ interacting protein ASPP2, another ASPP family member relative to ASPP1, was found to promote but not essential for TAZ-PP1 interaction. PP1 and ASPP2 decrease TAZ phosphorylation level and increase TAZ transcriptional activity [27]. ASPP2 interacts with TAZ and PP1A via the PPXY motif and RVXF motif, respectively.

ASPP1, but not IASPP (Inhibitor of ASPP protein, IASPP), also possesses a PPXY motif and a RVXF motif, implicating ASPP1, besides impeding TAZ-LATS complex formation [24], may also regulate TAZ phosphorylation level in a manner similar to ASPP2. Interestingly, both YAP1 and YAP2 can't bind with and be dephosphorylated by PP1. A recent study showed that ,at least in epidermal stem cells in mice, α-catenin regulates YAP1 activity and phosphorylation level by control YAP1's interaction with 14-3-3 and the PP2A phosphatase [28]. Thus it's worth noting that though the regulation mechanism of TAZ by Hippo pathway is similar to YAP's, the dephosphoryaltion step may be different, implicating the different function of TAZ/YAP and the need to precise control of TAZ/YAP during the development.

TAZ regulation independent of Hippo pathway

Besides Hippo pathway, many factors can regulate TAZ transcriptional activity through direct binding. Through its WW domain, TAZ was shown to bind with Polyomavirus T Antigens

[29]. Overexpression of TAZ inhibits viral replication, while Polyomavirus infection promotes nuclear translocation of TAZ but inhibits TAZ transactivation in a Gal4-TAZ luciferase assay [29]. How Polyomavirus inhibit TAZ transactivation in nucleus is not clear. AMOT (Angiomotin, AMOT) family members, previously identified being involved in maintaining tight junction, are also identified as strong interacting partners of TAZ and YAP [30, 31]. Binding to AMOT family members is critical for the localization of TAZ and YAP to the tight junction in MDCK cells [30]. Also, AMOT family members are negative regulators of TAZ and YAP, and this repression is independent of Hippo pathway's activity through direct binding with TAZ and YAP. Recently, the ECM (extracellular matrix, ECM) stiffness has been reported to regulate TAZ activity and localization, which is independent of Hippo pathway [32].

Through its PDZ-binding motif, TAZ can also bind with many PDZ domain containing proteins. Through their first PDZ domain, both ZO-1 (zona occludens 1, ZO-1) and ZO-2 (zona occludens 2, ZO-2) can interact with TAZ [33]. Only endogenous ZO-2 can partially colocalize with endogenous TAZ in the nucleus and inhibit TAZ's transcriptional activity. It is also first reported that the co-localization of TAZ and ZO-1 at the membrane in the CaCo-2 cells provides evidence for the localization of TAZ is cell context dependent [33]. Proteomic analysis of TAZ binding partners by TAP-MS/MS methods, reveals many PDZ-binding proteins, such as Crumbs complex components, including PALS1 (membrane protein, palmitoylated 5), LIN7C (lin-7 homolog C) and PATJ (protein associated to tight junctions, PATJ)/MPDZ (multiple PDZ domain protein, MDPZ) [25]. The Crumbs complex is a tight junction related component which localizes to the apical domain of polarized epithelial cells in high density. Genetic studies in *Drosophila* have shown that Crb (Crumb, Crb) influences the Salvador/Warts/Hippo (SWH) pathway and tissue growth, which is characterized by modulating expression of Ex (Expanded, Ex), an upstream regulator of Hippo [34, 35]. The mechanism regulating TAZ activity by Crumbs complex in mammals is different from in *Drosophila*. Both WW-domain and PDZ-binding motif are required for the interaction with PALS1, therefore, the Crumbs complex. Knockdown PALS1 or Crumb3 decreases Ser89 phosphorylation level and promotes nuclear localization of TAZ in the high density cells [25]. Conversely, PDZ-binding motif is important for TAZ transcriptional coactivator activity, since deletion of PDZ-binding motif also abolished TAZ-mediated transcriptional co-activation [1], indicating that a positive regulator or a modulator positively regulates TAZ's transcriptional activity is still unknown.

Transcription factors interacting with TAZ

Despite the similar regulation mechanism of TAZ and YAP by the Hippo pathway, TAZ and YAP, as transcriptional co-activator, bind with different transcription factors but also share some identical target transcription factors, particularly TEAD family members, suggesting that TAZ and YAP have partially different biological function and have redundant functions in some aspects. TAZ has been reported to interact with RUNX2 [3], TTF-1/Nkx-2.1 [9, 10], TBX5 [5], PPARγ [4], PAX3 [11], MyoD [36], PAX8 [10], Glis3 [37], SMAD2, SMAD3 [25, 38], and TEADs [6-8]. Through interacting with different transcription factors, TAZ performs diverse biological functions. TAZ was firstly identified as a transcriptional co-activator for RUNX2 by yeast two-hybrid system, promoting osteoblast specific expression, such as osteocalsin, and may be involved in osteoblast differentiation regulation [3]. Further study has found that TAZ is a crucial regulator of mesenchymal stem cell (mesenchymal stem cell, MSC) differentiation. TAZ can promote osteoblast differentiation by enhancing RUNX2 dependent transcriptional activation while repressing PPARγ dependent transcription, thereby inhibit adipocyte differentiation [4]. From then on, TAZ has been used as an important marker for indicating osteogenic potential [39-41]. FGF2, an osteogenic cytokine, surprisingly has been shown to decrease TAZ protein level and inhibit osteoblastic feature in MC3T3-E1 cells [42]. Thought the mechanism is still obscure, it demonstrates that TAZ is not only crucial for osteoblastic differentiation in MSC but also important for maintaining osteoblastic feature in osteoblast-like cells. The involvement of the Hippo pathway in regulating the MSC differentiation has not been shown but could be predictable and plausible. To induce adipocyte differentiation, 3T3-L1 cell should be grown to confluence first then induced in the differentiation medium [4]. Under high density, Hippo pathway is activated to phosphorylate TAZ at Ser89 and Ser311, which inhibits TAZ

activity by promoting cytoplasmic localization and proteosome-dependent degradation, thereby releasing PPARγ from repression by TAZ to activate adipogenic gene expression. Recently, Clenbuterol, a β_2-adrenoceptor agonist which is widely used to decrease the fat deposition in pig raising, has been shown to increase the pig Lats2 mRNA expression [43]. Also during the adipocyte differentiation in 3T3-L1 cells, mRNA of Lats2 is increasing significantly [43]. It's worth noting that PPARγ is the only transcription factor found to be inhibited by TAZ acting as a co-repressor until now. TAZ, acting as co-activator, is reported to recruit P300 and PCAF [5], which are histone acetyltransferases to enhance transcription in the presence of TAZ. How TAZ can function as both co-activator and co-repressor is still obscure, which may be dependent on DNA context at the promoter thus recruiting different histone modifier and mediator complex.

Besides its crucial function in regulating differentiation of MSC, TAZ has been shown to be important for other organ development. TAZ is expressed in the thyroid tissues and localizes in the nucleus of the differentiated thyroid follicular cells [10]. PAX8 and TTF-1, which are important transcription factors involved in thyroid development, have been demonstrated to interact with and be activated by TAZ. Co-localization of TAZ, PAX8 and TTF-1 is observed during the thyroid development and in the adult thyroid tissues [10]. Taz is also co-expressed with another transcriptional factor Pax3, interacting with Taz, in the paraxial mesoderm, limb buds and neural tube during mouse embryonic development [11]. This raises the possibility that Taz and Pax3 may contribute to regulate myogenic and neurogenic gene expression and cell differentiation. Besides Pax3, TAZ interacts with another myogenic transcription factor MyoD through WW domain [36]. TAZ is translocated to nucleus during the myogenic differentiation to enhance MyoD dependent myogenic gene expression, such as myogenin. Thus, TAZ is also a crucial modulator in myoblast differentiation which is another lineage of MSC.

Transforming growth factor β (TGFβ) family and bone morphogenetic protein (BMP) family cytokines play a crucial role in embryo morphogenesis and adult tissue homeostasis through regulating their nuclear effectors SMAD Proteins. The crosstalk between the Hippo pathway and TGFβ/BMP pathway has been shown in mammals. Through WW domain, YAP interacts with phosphorylated SMAD1 under BMP stimulation, which promotes self-renewal capability of mESCs (mouse embryonic stem cells, mESCs) [44]. SMAD7 is an inhibitory effector of TGFβ pathway, through interacting with SMAD7, YAP1 can augment SMAD7 function as an antagonist of TGFβ signaling [45]. Interestingly, TAZ has been shown to interact with SMAD2 and SMAD3 through its coiled-coiled domain under TGFβ stimulation [38]. This interaction is crucial for nuclear localization of SMAD2/3 and maintaining human embryonic stem cells (hESCs) self-renewal but not mESCs [38], in which Smad1/5/8 signaling is important for maintaining the pluripotency. Given the fact that TAZ modulates nuclear localization of SMAD2/3 through direct binding, the Hippo pathway and Crumbs complex has been shown to regulating SMAD2/3 localization through TAZ [25]. It's interesting to note that TAZ itself nuclear localization is in some extent dependent on the interaction with its transcriptional binding partners, since many transcription factors interacting with TAZ can promote TAZ nuclear localization. For instance, overexpression of RUNX2 [3], Glis3 [37] or TEAD [7] promoted nuclear retention of ectopically expressed TAZ. This raises an interesting possibility that whether other transcription factors regulate SMAD2/3 signaling through TAZ.

TAZ also contributes to control adult tissue homeostasis. Overexpression of TAZ promotes cell proliferation, cell migration, transforming and EMT in normal mammary MCF10A cells [15, 18]. Among multiple transcription factors binding with TAZ, TEADs, homologs of *Drosophila* Sd (scalloped, sd) protein, are the prime mediators of the TAZ/YAP function in the Hippo pathway. Both knockdown of TEADs and mutation of TAZ disrupting the interaction between TAZ and TEADs diminish TAZ function in cell proliferation, cell migration, transforming and EMT [8]. CTGF (Connective tissue growth factor, CTGF), a cytokine important for cell growth and development, has been shown a direct target of TAZ/YAP/TEAD, which is significant for TAZ function in promoting cell proliferation [8, 46]. Recently, studies show that another direct target of TAZ/TEAD, Cyr61 (cysteine-rich, angiogenic inducer 61, Cyr61) cooperatively acts with CTGF to render taxol resistence to breast cancer cell overexpression of TAZ [47]. The TAZ/TEAD direct target

gene involved in promoting cell migration and EMT is still missing. Though a recently study has reported ZEB1 (zinc finger E-box binding homeobox 1, ZEB1), a key regulator of EMT, is direct target gene of TAZ/TEAD1 in retinal pigment epithelial cells [48]. Further studies should be performed to confirm the ZEB1's expression in mediating TAZ function in EMT. It's worth noting that TGFβ signaling pathway is important for TAZ's function in EMT (unpublished data). AREG (Amphiregulin, AREG) is a direct target of YAP to enhance non-cell-autonomous proliferation [49], which is also activated by TAZ activation [8], implicating TAZ/YAP share another important unknown transcription factor mediating their biological function.

WW domain of TAZ is crucial for transforming in MCF10A cells. Interestingly, both ITGB2 (integrin beta 2, ITGB2) and CTGF are TAZ direct target genes dependent on TEAD, but mutation of WW domain of TAZ diminishes ITGB2 expression, indicating that other factors can modulate TAZ/TEAD transcriptional outcome through interacting with WW domain of TAZ [50]. WBP2, a previous identified as YAP1 binding partner, has been shown to bind with TAZ and enhance transforming activity of TAZ through its PPXY motif [50]. This regulation is conserved in *Drosophila. Drosophila* Wbp2 (WW domain binding protein 2, Wbp2) also interacts with Yki in a manner dependent on the WW domain and PPXY motif and regulate Yki transcriptional activity [51]. This implicates WBP2, targeted by other signaling pathway, can regulate the Hippo pathway. Interesting, WBP2 was also shown to be a binding partner of thyroid specific transcription factor PAX8, but does not affect PAX8 transcriptional activity when overexpressed alone [52]. The deletion of the C-terminal amino acids disrupts the interaction with both WBP2 and TAZ [52]. It will be interesting to explore whether TAZ cooperates with WBP2 to regulate PAX8 dependent gene expression and thyroid differentiation.

Non-nuclear function of transcription coactivator TAZ

In addition to its nuclear transcriptional activity of TAZ, cytoplasmic TAZ also possesses activity independent of its transcriptional activity, which is common in p53 [53]. Cytoplasmic TAZ can compete binding to Dvls (dishevelled, dsh homologs, DVLs) with CK1 and decrease Dvl2 phosphorylaton by CK1, thereby promote assembly of so called "β-catenin destruction complex" and β-catenin degradation [54]. Knockdown endogenous TAZ increases β-catenin protein level and Wnt target gene expression, while MST and LATS can modulate Wnt signaling by regulating TAZ phosphorylation and cytoplasmic localization [54]. This crosstalk between the Hippo pathway and the Wnt pathway is conserved in *Drosophila*, in which loss of Yki function leads to expression of Wingless target genes [54].

Phosphorylation by LATS and CK1 promotes TAZ degradation by recruiting the $SCF^{\beta\text{-}TrCP}$ E3 ligase [20]. PC2 (polycystin 2, PC2) is a nonselective calcium permeable cation channel protein [13]. Interestingly, TAZ itself can also target PC2 to $SCF^{\beta\text{-}TrCP}$ E3 ligase as a substrate recruiter and a component of the E3 ligase. Knockout *Taz* in mice results in overexpression of PC2 in renal cells. Recently, Nek1 (never in mitosis gene a-related kinase 1, NEK1) has been reported to phosphorylate TAZ for PC2 degradation [55]. More interestingly, they also found that TAZ target Nek1 degradation [55]. This mechanism extents the biological function of TAZ and targeting efficiency of the same E3 ligase [56].

Physiological role of TAZ in development

To investigate the *in vivo* physiological function of TAZ, *Taz* knockout mice were generated [12-14]. But, surprisingly, *Taz* knockout mice just suffer a minor skeletal defect though TAZ plays a crucial role in MSC differentiation. Interestingly, *Taz* knockout mice develop two severe abnormalities: PKD (polycystic kidney disease, PKD) and emphysema, implicating TAZ plays a crucial role in renal development and lung development [12-14]. PKD is a leading cause of end-stage renal disease. Renal cyst development in *Taz* knockout mice is accomplished with cilia defect and downregulation of gene expression related to PKD, such as KIF3A (kinesin family member 3A, KIF3A), PKHD1 (polycystic kidney and hepatic disease 1, PKHD1) [12]. There are several mechanisms implicating the development of PKD in *Taz* knockout mice, but the main mechanism underlying developing PKD need to be explored. In human, ADPKD (autosomal dominant polycystic kidney disease, ADPKD) is due to mutations in PKD1 and PKD2 which encode the transmembrane proteins PC1 (polycystin 1, PC1) and PC2 [57]. Both reduced expression [58] and overexpression of PC1 [59] result in PKD development. TAZ has been

shown not only itself to be the target of $SCF^{\beta\text{-}TrCP}$ but also to recruit PC2 to $SCF^{\beta\text{-}TrCP}$ E3 ligase promoting PC2 degradation [13]. Knockout of *Taz* is coupled with renal cystic formation and overexpression of PC2 both in Zebrafish and mice, which disrupts the balance between PC1 and PC2 and affects the ion transport function of the PC1/PC2 complex [13]. Recently, an additional and more direct mechanism has demonstrated TAZ is a negative regulator of PC2 channel activity which is enhanced by PATJ(Protein associated to tight junctions, PATJ) through interacting both TAZ and PC2 [60]. Ectopic activation of the Wnt signaling has been related to PKD. Studies show that either constitutive expression of active β-catenin [61] in kidney or deletion of APC (adenomatous polyposis coli, APC) preventing β-catenin degradation [62] results in PKD. TAZ is a negative regulator of Wnt signaling and knockout *Taz* in kidney has been shown to result in mislocalization of β-catenin in kidney cysts and increased stability of β-catenin [54]. Those data suggests that β-catenin could be the third cause of PKD in *Taz* knockout mice. Defect of ciliagenesis has been shown to be related to PKD, knockdown TAZ in the renal epithelial cell resulted in loss of cilia integrity suggesting the important role of TAZ in maintaining the renal cilia integrity and kidney development [12]. Components of tight junction, such as Crumb3, have been found to regulate ciliagenesis through association with microtubules and the microtubular motor KIF3/Kinesin-II [63]. Given the fact that TAZ interacts with Crumb3 complex, TAZ may directly regulate ciliagenesis through polarity proteins. The expression levels of several genes related to PKD were downregulated in *Taz* knockout mice, this raises the possibility that loss of transcriptional activity of TAZ is involved in developing PKD. Interestingly, knockout of *Glis3* also results in PKD in mice and Glis3 can interact with TAZ in a manner dependent on WW domain and PPXY motif [37]. But genes downregulated in *Glis3* knockout mice related to PKD [37] are not the same as those in *Taz* knockout mice, so how the Glis3 and Taz cooperate in developing PKD is not clear.

TAZ function in development of carcinomas

TAZ has also been implicated in human tumorigenesis. Notably, elevated TAZ expression was observed in over 20% breast cancer samples, especially in the IDC (invasive ductal carcinomas, IDC) [15], indicating TAZ function in metastasis and increasing the malignancy of breast cancer. Recently, two studies have connected TAZ overexpression with the development of the NSCLC (non-small cell lung cancer, NSCLC) [64] and PTC(papillary thyroid carcinoma, PTC) [65]. TAZ is overexpressed in the NSCLC cell lines and knockdown TAZ significantly impaired the tumorigenic ability of the NSCLC cells [64], but the NSCLC clinical samples should be explored in the future. The transcripts of TAZ from 61 samples of PTC were examined and found to be overexpressed significantly [65]. That raises the implication that though TAZ and YAP is inhibited by the Hippo pathway, which contains well-established human tumor suppressor NF2, and WW45 and Mob that are mutated in human cancer cell lines, dysregulation of mRNA expression and other mechanisms may contribute the dysfunction of TAZ and YAP in human cancer. It's true that overexpression of YAP and TAZ are not overlapped with each other in human cancers [15]. More studies need to explore the transcriptional regulation of TAZ expression. Studies have reported that TAZ expression is correlated with many stimulus. TGFβ and BMP treatment increase the expression of TAZ [4, 38]. Furthermore, RAS activation in a rat thyroid cells elevates the expression level of TAZ [65]. A recent study also shows that TAZ is a direct target of NF-κB promoting osteoblast differentiation responding to TNF-α [40].

Perspective

Over the past decade, our understanding of TAZ function in embryo development, stem cell differentiation and cancer progression has largely increased. More and more evidences indicate that TAZ is functionally similar to β-catenin [66]. When TAZ enters nucleus, TAZ interacts with downstream transcription factors to regulate gene expression. Besides its nuclear function, TAZ also possesses function in the cytoplasm and localizes in the membrane in a cell context dependent manner, which may be important for the regulation of ciliagenesis and other unknown function. The mechanisms of TAZ regulation is also described and explored widely. But the *in vivo* physiological function of TAZ in development and cancer progression still need to be examined. For example, as the prime transcriptional factor mediating the function of TAZ and given the important function in development, Ser51A knock-in mice, which mutant disrupts

the interaction between TAZ and TEADs, need to be generated to explore involvement of TEADs in the physiological function of TAZ in development. Also Ser89A knock-in mice should be generated to examine contribution of the elevated TAZ activity in cancer development and progression. The existence of not-yet unidentified regulators of TAZ and downstream transcription factors as well as new direct target genes implicating in new function of TAZ need to be explored. Future studies of TAZ will not only deep our understanding the normal development regulation in organisms but also help to develop new cancer treatment.

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