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Trends in Biochemical Sciences

Review

YAP and TAZ Are Not Identical Twins

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Yes-associated protein (YAP) and TAZ (WW domain containing transcription regulator 1, or WWTR1) are paralog transcriptional regulators, able to integrate mechanical, metabolic, and signaling inputs to regulate cell growth and differentiation during development and neoplastic progression. YAP and TAZ hold common and distinctive structural features, reflecting only partially overlapping regulatory mechanisms. The two paralogs interact with both shared and specific transcriptional partners and control nonidentical transcriptional programs. Although most of the available literature considers YAP and TAZ as functionally redundant, they play distinctive or even contrasting roles in different contexts. The issue of their divergent roles is currently underexplored but holds fundamental implications for mechanistic and translational studies. Here, we aim to review the available literature on the biological functions of YAP and TAZ, highlighting differential roles that distinguish these two paralogues.

Highlights

YAP and TAZ are transcription coactivators that display both common and specific features that support not completely overlapping cell functions.

Structural differences between YAP and TAZ support the interaction with specific transcriptional partners, which contribute to divergent transcriptional programs.

YAP and TAZ activity is tightly regulated by distinct alternative splicing events, common and specific post-translational modifications, and shared and differential regulatory mechanisms.

YAP and TAZ are central hubs in gene expression, integrating multiple extracellular and intracellular inputs to control both embryogenesis and cancer progression through specific context-dependent mechanisms.

YAP and TAZ Play Common and Distinct Roles

Since the discovery of YAP by Sudol in 1994 [1], transcriptional regulators YAP and TAZ have become the focus of extensive research for their consolidating role in development and disease. In *Drosophila*, Yorkie, the ortholog of mammalian YAP and TAZ, has been identified as the main effector of the Hippo cascade of kinases, regulating larval tissues growth [2]. During vertebrate evolution, a duplication event led to the diversification of two Yorkie orthologs, YAP and TAZ. These two paralogs retain remarkable similarities, but also distinctive features, suggesting a partial but not complete functional redundancy (Figure 1).

Both proteins act as transcriptional regulators even if lacking a DNA-binding domain. Their transcriptional activity is mediated by the interaction with **TEA domain** (TEAD) (see Glossary) and other transcription factors (see following text) [3,4]. The Hippo cascade of kinases, comprising **mammalian STE20-like protein kinase (MST)1/2** and **large tumor suppressor kinase (LATS)1/2** in mammals, is the classical mechanism that negatively regulates YAP and TAZ activity by promoting their cytoplasmic retention and/or degradation. In a recent and most comprehensive version of this classical model, multiple pathways converge on YAP and TAZ regulation, balancing their nuclear/cytoplasm shuttling and defining the overall extent of their nuclear accumulation and consequentially their transcriptional activity [5].

In the past 20 years, YAP and TAZ have emerged as central hubs of complex cell and organ regulatory networks, integrating mechanical, metabolic, extracellular and intracellular signaling to dictate cell growth, differentiation and malignancy (Boxes 1 and 2). However, many aspects of their activity and regulation are still poorly defined, including the characterization of their specific functions. Unfortunately, in many cases, data on the biological function of only YAP or only TAZ are available, often without considering the potential interplay or juxtaposition between the two paralogs.

The notion that YAP and TAZ have both overlapping and distinctive functions is supported by several studies that investigated the consequences of their loss or gain of function in either cellular

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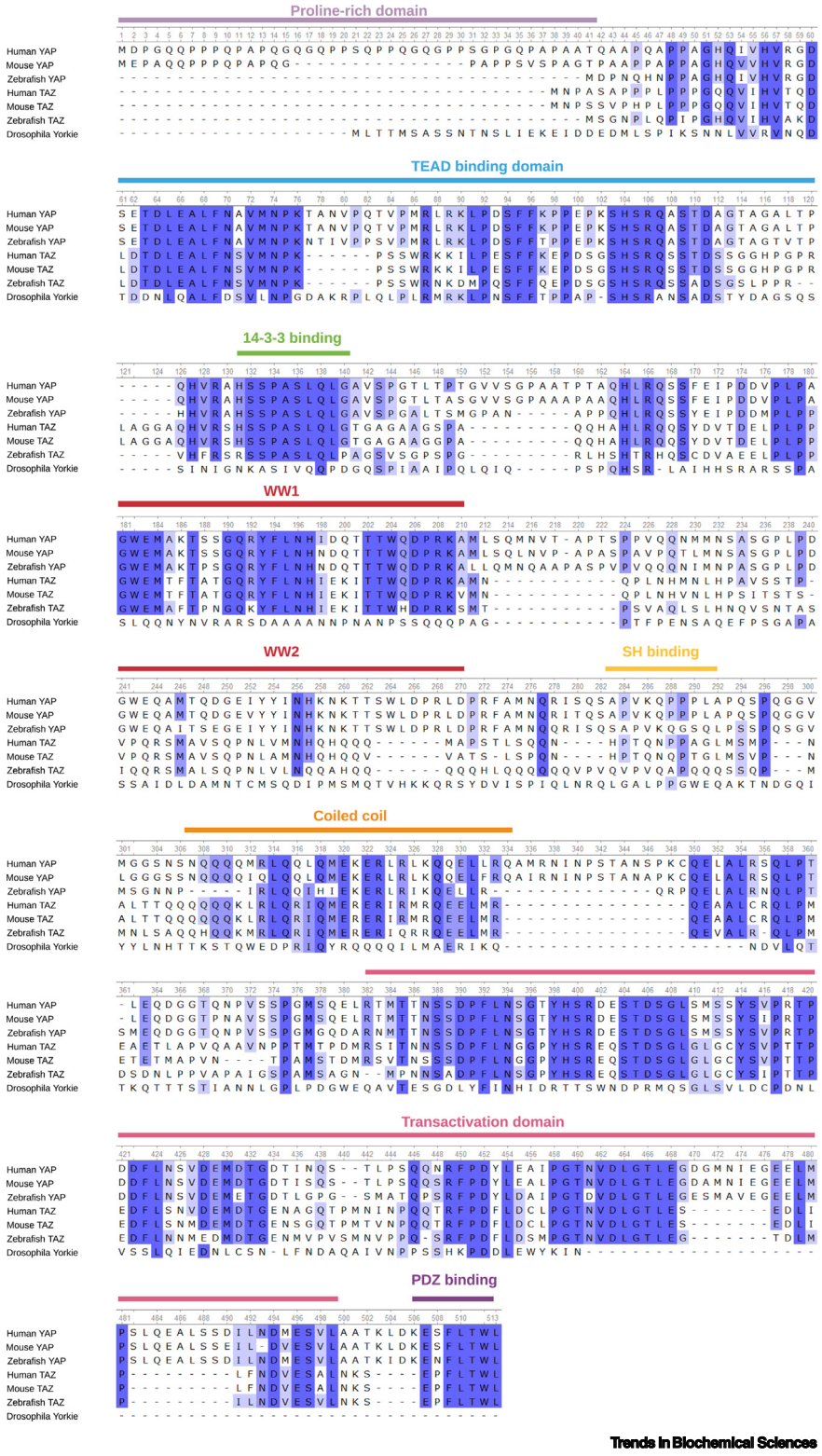

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Glossary

14-3-3: family of proteins involved in signal transduction.
Angiomotins (AMOTs): family of proteins, part of tight junctions.
Bromodomain containing 4 (BRD4): member of the bromodomain and extraterminal domain family.
c-JUN: Jun proto-oncogene, subunit of the AP-1 transcription factor.
Casein kinase 1 (CK1): participates in WNT signaling as an integral part of the destruction complex.
β-Catenin: product of the *CTNNB1* gene, part of cell–cell adhesion complexes and major player of WNT pathway.
CRK: CRK proto-oncogene, adaptor protein, adaptor protein containing a SH2 and a SH3 domain.
Crumbs: transmembrane proteins with a key role in epithelial cell polarity.
Cyclin-dependent kinase 9 (CDK9): a component of the TAK/P-TEFb complex, which phosphorylates RNA Pol II.
G-protein coupled receptors (GPCRs): family of transmembrane receptors, signaling through G-proteins.
Glycogen synthase kinase 3α (GSK3): participates in WNT and PI3K signaling.
HCK: HCK proto-oncogene, SRC family tyrosine kinase.
Large tumor suppressor kinase 1 and 2 (LATS1/2): homologs of *Drosophila* Warts.
Mammalian STE20-like protein kinase 1 and 2 (MST1/2): homologs of *Drosophila* Hpo.
Mediator of RNA Pol II transcription subunit 1 (MED1): a subunit of the Mediator complex.
MOB kinase activator 1A and B (MOB1A/B): homolog of Drosophila Mats.
Na^+/H^+ exchange regulatory cofactor (NHERF): scaffold protein that connects plasma membrane with cytoskeleton.
Neurofibromin 2 (NF2): homolog of *Drosophila* Merlin, is a cytoskeletal scaffold protein, linking actin filaments with cell membrane.
Noncatalytic region of tyrosine kinase (NCK): adaptor protein containing SH2 and SH3 domains.
p300/CBP: two related transcriptional coactivators and histone acetyltransferases.

Box 1. Complementary Functions of YAP and TAZ in Development

The Hippo pathway is universally considered a potent regulator of organ development, homeostasis and regeneration. In the majority of studies, high levels of YAP/TAZ promote stemness and inhibit differentiation, leading to increased organ size and other abnormalities [6].

However, differences in phenotypes of KO mice support distinctive functions of the two paralogs during development. KO of YAP leads to embryonal lethality with yolk sac vasculogenesis defects and embryonic axis abnormalities [9]. Conversely, TAZ KO mice are viable, but develop kidney disease and lung emphysema [10,11].

These results establish a very specific role for TAZ in kidney and lung. Strikingly, kidney-restricted KO of YAP reveals a different phenotype, associated with impaired nephrogenesis with hypoplastic and nonfunctional kidneys [77]. A similar situation, in which both paralogs are involved in organ development but with complementary functions, occurs in lung. YAP is required for bronchial morphogenesis at embryonic stage, whereas TAZ ablation leads to abnormal alveolarization, mimicking lung emphysema [78,79].

In skeletal muscle, both factors promote proliferation of satellite cells, the stem cells pool resident in skeletal muscle. In addition, TAZ promotes and potentiates MyoD-induced myogenic differentiation, whereas YAP prevents this process [80–82].

In the mammary gland, TAZ, but not YAP, is crucial for lineage commitment. TAZ is nuclear and active only in basal cells [83]. Forced TAZ expression in luminal cells promotes the acquisition of basal features, whereas TAZ downregulation in basal cells induces a luminal-like phenotype. On the contrary, the role of YAP seems to be limited to modulate alveoli terminal differentiation during pregnancy [84].

The finding that YAP KO mouse embryos show yolk sac vasculogenesis defects that cannot be compensated by TAZ, points to a differential role of YAP and TAZ in regulating blood vessels formation [9]. Indeed, YAP and TAZ have distinct expression and localization in endothelial cells (ECs) [85,86]: nuclear TAZ is mainly expressed in the sprouting front of growing vessels, whereas YAP is mostly cytoplasmic both in sprouting and mature vessels. In this context, YAP mainly affects EC proliferation whereas TAZ has a major role in promoting migration [86].

Intriguingly, the main phenotype of ubiquitously overexpressing YAP mice is obesity. This phenotype is determined by TAZ inhibition which is induced by hyper-activation of YAP. In this model, TAZ attenuation induces adipogenesis, in accordance with the mentioned function of TAZ as transcriptional repressor of adipocyte differentiation [42,56].

Salvador family WW domain containing protein 1 (SAV1): homolog of *Drosophila* Salvador.
Scribble: homolog of *Drosophila* Scribble is involved in epithelial cells polarity.
SET domain containing 7 (SETD7): histone lysine methyltransferase showing also methyltransferase activity on nonhistone targets.
Signal transducer and activator of transcription 1 (STAT1): key transcription factor of the JAK/STAT pathway.
Silent mating type information regulation 2 homolog 1 (SIRT1): NAD-dependent deacetylase.
SRC proto-oncogene: non-receptor tyrosine kinase.
SRC homology 3 domain (SH3): protein–protein interaction domain, frequently found in tyrosine kinases.
Switch/sucrose nonfermentable (SWI/SNF): a family of ATP-dependent chromatin remodeling complexes.
TEA domain (TEAD): homologs of *Drosophila* Scalloped.
β-Transducin repeat containing E3 ubiquitin protein ligase (β-TrCP): a member of SCF complexes.
β-TrCP: beta-transducin repeat containing E3 ubiquitin protein ligase, a member of SCF complexes (SKP1-cullin-F-box).
WNT: wingless-type MMTV integration site signal transduction, group of signaling pathways important in embryonal development and carcinogenesis.
YES proto-oncogene 1 (YES): Src family tyrosine kinase.
Zonula occludens 1/2 (ZO1/2): membrane-associated proteins involved in tight and adherens junctions.

or animal models [6–8]. YAP knockout (KO) mice are not viable, showing embryonal lethality around E8.5 with yolk sac vasculogenesis defects and embryonic axis abnormalities [9]. On the contrary, TAZ KO mice are viable, but develop kidney and lung diseases [10,11] (Box 1).

Here, we review several aspects of YAP and TAZ biology to highlight the relevant differences between these two factors, from structural features to regulatory mechanisms and transcriptional partners. These distinctive features represent the basis to understand the nonoverlapping roles of YAP and TAZ in both physiological development and cancer (Boxes 1 and 2). Reporting the emerging evidence of distinct functions of YAP and TAZ will help to clarify the multifaceted context-dependent behavior of the two paralogs, with the final goal of summarizing the available knowledge and stimulating further research on this topic.

Structural Similarities and Differences between YAP and TAZ

Protein Domains

Human YAP and TAZ reference sequences show about 40% amino acid conservation and share several structural features, whereas other characteristics are distinctive (Figure 1). Due to the lack

Figure 1. Alignment of YAP and TAZ Protein Sequences. Alignment of YAP and TAZ reference protein sequences from different vertebrates and Drosophila Yorkie. Blue highlights amino acid conservation, ranging from the less conserved residues (light blue) to the most conserved regions (dark blue). The main protein domains are indicated above the alignment. Abbreviations: PDZ, PSD-95, Dlg1, ZO-1; SH, SRC Homology; TAZ, WW domain containing transcription regulator 1; TEAD, TEA domain; WW1, WW domain 1; WW2, WW domain 2; YAP, Yes-associated protein.

Box 2. Differential Roles of YAP and TAZ in Cancer

Many cancers are addicted to YAP and TAZ oncogenic functions, which support tumor proliferation, survival, migration, drug resistance, EMT, and cancer stem cell (CSC) properties [76,87,88]. However, YAP and TAZ exert complementary, differential or even opposite roles in tumor progression, suggesting that tumor genetic background, cell and tissue contexts may affect YAP and TAZ functions.

TAZ seems to be more relevant than YAP in lung cancer, being TAZ overexpression sufficient to induce transformation of bronchial epithelial cells [89]. Conversely, YAP promotes lung tumor progression only when driven by *KRAS* or *LKB1* mutations [90]. YAP and TAZ control nonoverlapping transcriptional programs: YAP supports cell division and cell cycle progression, whereas TAZ controls migration and ECM remodeling [8]. High expression of TAZ, but not of YAP, is associated with poorer prognosis in lung adenocarcinoma patients [8,91]. Indeed, TAZ has been shown to drive brain metastases [92], possibly explaining the poorer patients' outcome associated with TAZ.

YAP is the key driver in hepatocellular carcinoma (HCC), in which YAP, but not TAZ, overexpression is associated with negative patients' prognosis [93]. Accordingly, YAP KO impairs HCC cell growth to a greater extent than TAZ [93]. In mouse models, overexpression of YAP, but not of TAZ, increases liver cancer development and impairs overall survival [41]. However, TAZ may have a role in a subgroup of highly aggressive HCC, characterized by the absence of keratin 19: the nuclear localization of TAZ, but not of YAP, is associated with a worse prognosis in these patients [94].

Both YAP and TAZ are essential for BC, but controlling distinct functions. While TAZ is highly expressed in BC cell lines, YAP is similarly expressed in BC and normal epithelial cells [37]. Furthermore, TAZ expression is higher in invasive BC cells, whereas YAP levels are not associated with tumor invasiveness [95]. TAZ enhances CSC-like phenotype and its expression predicts poor outcome in scarcely differentiated BC patients [37]. By contrast, YAP but not TAZ cooperates with mutant p53 in driving BC progression [96].

The differential role of YAP and TAZ is exacerbated in hematological malignancies, in which, unlike TAZ, YAP has been frequently identified as tumor suppressor. Low YAP expression is predictive of poor outcome in lymphoma, leukemia and multiple myeloma [73]. YAP–ABL1–p73 interaction triggers DNA damage-induced apoptosis, improving therapy response [73].

of DNA-binding domain, YAP and TAZ rely on interaction with other factors to execute their transcriptional activity.

The most prominent shared structural feature is the WW domain, consisting of two tryptophan residues separated by 20–23 amino acids. The WW domain is a protein–protein interaction domain, which recognizes the PPxY motif (proline/proline/any amino acid/tyrosine) that is present in a variety of proteins, including many transcription factors and regulatory proteins known to be YAP/TAZ interactors [e.g., Runt-related transcription factor (RUNX), activating protein (AP)-2, **c-JUN**, LATS, and **angiomotins** (AMOTs)]. TAZ has only one WW domain, whereas YAP bears two, although YAP splicing isoforms lacking the second WW domain have been reported (see following text) (Figure 2A) [12]. The presence of one or two WW domains may affect the set of distinct YAP and TAZ interactors and/or establish different interaction modalities, since the two WW domains can simultaneously bind two PPxY motifs.

The second important shared feature is the TEAD-binding domain, located N-terminal to the WW domain. In YAP, this domain consists of two α helices connected by a loop harboring a PxxΦP motif (where x is any amino acid and Φ is a hydrophobic residue) [13–15]. Although the TEAD-binding domain is relatively well conserved among the two paralogs, TAZ lacks the PxxΦP motif (Figure1). Indeed, structural studies reveal that the two paralogs bind TEAD with similar affinities but different modalities. Both YAP and TAZ form heterodimers with TEAD. In addition, two TAZ molecules can criss-cross each other to bring two TEAD molecules together, thus forming a heterotetramer (Figure 2B) [16]. The work of Murakami and colleagues further supported the ability of TAZ to form homodimers and heterodimers with YAP, whereas YAP lacks the ability to homodimerize [17]. The ability of TAZ–TEAD complexes to form heterotetramers suggests the possibility to bind DNA sites bearing multiple TEAD binding sites with different affinity, compared to YAP–TEAD or TAZ–TEAD heterodimers.

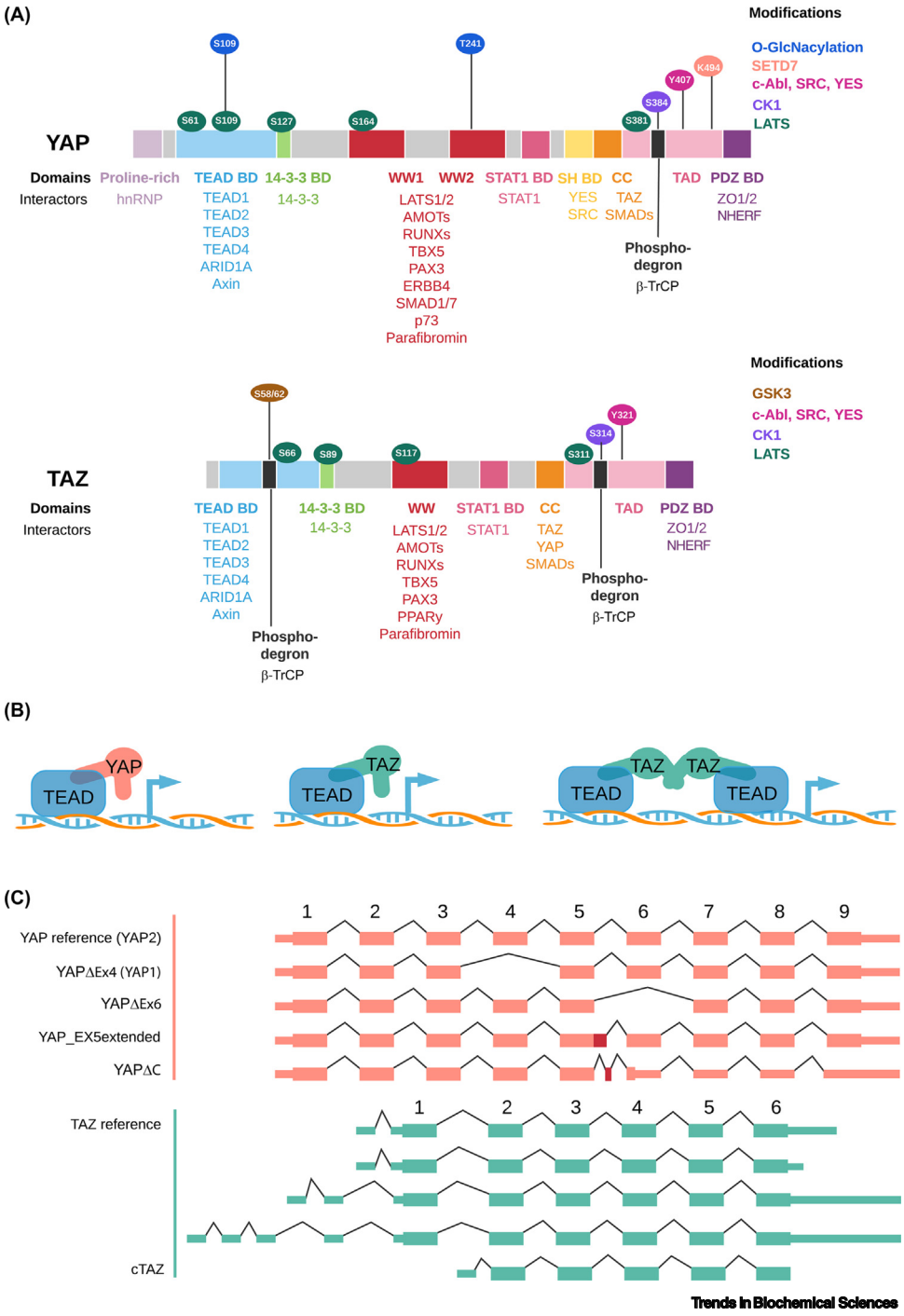

Figure 2. YAP and TAZ Structural Differences. (A) Schematic representation of YAP and TAZ protein domains, with relevant interactors of each domain. The main post-translational modification sites with relevant enzymes are reported above each scheme. Amino acid numbers are reported according to human sequences. (B) YAP forms a heterodimer with TEAD, while TAZ–TEAD complexes can exist as both heterodimers or heterotetramers. (C) Schematic representation of YAP (pink) and TAZ (green) differential transcripts. Exons are represented as boxes and introns as lines. 5′ UTR and 3′ UTR regions are represented as lower boxes. Exon 5 extended region and additional nucleotides inserted between

(Figure legend continued at the bottom of the next page.)

The third main shared feature is the C-terminal transactivation domain, consisting of an unstructured domain, which mediates transcription activation. The C-terminal end of both paralogs displays a PDZ-binding domain, which is necessary for nuclear localization and has been shown to bind **zonula occludens 1/2** and **Na^+/H^+ exchange regulatory cofactor (NHERF)** proteins [3,4]. YAP and TAZ also share a coiled-coil domain located upstream of the transactivation domain, implicated in protein–protein interactions (Figure 2A).

Among the structurally distinctive features that differentiate these proteins, there is a proline-rich motif at the N-terminal end of YAP, which is not conserved in TAZ. This region interacts with heterogeneous nuclear ribonucleoprotein U [18], a protein implicated in pre-mRNA splicing. This interaction takes place exclusively in the nucleus and, as a consequence, YAP transcriptional activity is inhibited (Figure 2A). Differently from TAZ, YAP also harbors an **SRC homology 3 domain** (SH3)-binding motif (amino acids PVKQPPPLAP), which is located between the WW and the coiled-coil domains. This region mediates interactions with the SH3 domain of several proteins, including the **YES** and **SRC** kinases, as well as the adaptor proteins **noncatalytic region of tyrosine kinase (NCK)**, **CRK**, and **HCK** [1,3,4], increasing and differentiating the panel of potential partners of YAP.

Alternative Splicing

Alternative transcripts have been described for both YAP and TAZ. YAP reference transcript comprises nine exons, of which exons 4 and 6 can be alternatively spliced (Figure 2C). Exon 4 encodes the second WW domain, while exon 6 is part of the transactivation domain. In addition, exon 5 has an alternative 3′ donor splice site generating a 12 bp longer exon [12]. Neuronal-specific isoforms of YAP have been described, being generated by the insertion of a variable number of nucleotides between exons 5 and 6. These insertions lead to translation frameshifts and to the production of a truncated version of YAP (YAPΔC), lacking the transactivation domain (Figure 2C). In neurons, YAPΔC isoforms are prosurvival factors, acting as dominant negative towards full-length YAP, which, together with p73, controls a paradoxical proapoptotic transcriptional program [19,20].

Human TAZ displays six coding exons and multiple transcripts, which mainly differ in their transcription start site and 3′ untranslated region (UTR) length, indicating the possible regulation of TAZ mRNA synthesis and stability (Figure 2C). Notably, an alternative promoter-derived isoform encodes a truncated TAZ protein (cTAZ), lacking both the TEAD-binding domain and the WW domain (Figure 2C). This isoform is not subjected to Hippo pathway regulation and suppresses JAK–STAT signaling through direct interaction with **signal transducer and activator of transcription 1 (STAT1)** (Figure 2C) [21]. The presence of distinct mechanisms for generating alternative isoforms, that are not shared between YAP and TAZ, adds paralog-specific layers of regulation and underlines how these two genes diverged in structure, possibly leading to functional divergency.

exon 5 and exon 6 of YAP are depicted in red. In addition to papers cited throughout the text, we took advantage of the data available in Ensembl (https://www.ensembl.org/) and Genome Browser (https://genome.ucsc.edu/) public databases. Abbreviations: AMOTs, angiomotins; ARID1A, AT-rich interactive domain-containing protein 1A; BD, binding domain; CC, coiled coil; CK1, casein kinase 1; ERBB4, erb-b2 receptor tyrosine kinase 4; GSK3, glycogen synthase kinase 3α; hnRNP, heterogeneous nuclear ribonucleoprotein; LATS1/2, large tumor suppressor kinase 1 and 2; NHERF, Na(+)/H(+) exchange regulatory cofactor NHE-RF1; paired box gene 3; PDZ, PSD-95, Dlg1, ZO-1; PPARγ, peroxisome proliferator-activated receptor γ; RUNX, Runt-related transcription factor; SETD7, SET domain containing 7; SMAD1/7, small mother against decapentaplegic 1/7; SRC, SRC proto-oncogene, nonreceptor tyrosine kinase; STAT1, signal transducer and activator of transcription 1; TAD, trans activation domain; TAZ, WW domain containing transcription regulator 1; TBX5, T-box transcription factor 5; TEAD, TEA domain; β-TrCP, β;-transducin repeat containing E3 ubiquitin protein ligase; UTR, untranslated region; YAP, Yes-associated protein; ZO1/2, zonula occludens 1/2. YES, YES proto-oncogene 1.

Post-translational Modifications

YAP and TAZ activity is strictly regulated by several post-translational modifications that control their intracellular localization (Figure 2A). Phosphorylation of serine residues is the major switch of YAP/TAZ function, leading to **14-3-3** proteins binding, cytoplasmic retention and inactivation of their transcriptional activity [22].

Between the TEAD-binding domain and the WW domain, YAP and TAZ share a conserved serine (S127 on YAP and S89 on TAZ), which is the main target of **LATS1/2** phosphorylation and binding site for 14-3-3 proteins. Furthermore, LATS1/2 can phosphorylate four additional serine residues on YAP and three on TAZ. In particular, phosphorylation of S381 on YAP and S311 on TAZ induces the additional phosphorylation by **casein kinase 1 (CK1)**, generating a phosphodegron, which is recognized by **β-TrCP (β-transducin repeat containing E3 ubiquitin protein ligase)**, leading to YAP/TAZ polyubiquitylation via SKP1–cullin–F-box (SCF) E3 ubiquitin ligases and to the consequent proteasome degradation [3,4].

Notably, a second phosphodegron is present on TAZ but not on YAP. S58 and S62 can be phosphorylated by **glycogen synthase kinase 3α (GSK3)**, creating a binding site for β-TrCP and leading to TAZ degradation through the SCF/β-TrCP ubiquitylation pathway [23]. The presence of this second phosphodegron, may account for the lower stability of TAZ compared to YAP and for its higher tendency to be regulated by degradation mechanisms [24,25].

On the contrary, phosphorylation on tyrosine 407 on YAP (Y321 on human TAZ) seems to have a more complex role. This residue can be targeted by various kinases, including c-Abl, SRC, and YES1, and influences the interaction with transcriptional partners, ultimately leading to transcription activation or repression, depending on the context [26–29]. In addition, YAP, can be monomethylated, acetylated, or glycosylated with the addition of O-linked β-N-acetylglucosamine (O-GlcNAcylation) (see following text for details) [30–34].

Common and Differential Regulatory Mechanisms

Common Regulatory Mechanisms

The most classical regulatory mechanism of YAP/TAZ activity is the Hippo cascade of kinases and regulatory proteins [3,4]. The MST1/2 kinases are activated by the binding of their regulatory protein **SAV1 (Salvador family WW domain containing protein 1)** and phosphorylate LATS1/2 kinases, which are in turn activated. LATS1/2 form a complex with regulatory subunits **MOB kinase activator 1A and B (MOB1A/B)** and phosphorylate YAP and TAZ. When the Hippo pathway is active, YAP and TAZ are phosphorylated, leading to cytoplasmic retention and/or proteasomal degradation, with the consequent abolition of their transcriptional activity [3,4]. Nuclear YAP/TAZ associate with TEAD family and other transcription factors to activate specific transcriptional programs [3,4].

YAP/TAZ activity is tightly controlled by cell shape and extracellular matrix (ECM) stiffness since a stretched cell shape and a stiff ECM promote their nuclear relocalization [35]. This phenomenon is dependent on cytoskeletal integrity and properly structured F-actin [36]. Different membrane-associated components, including **neurofibromin 2 (NF2)**, **Crumbs**, and **Scribble** complexes, transduce extracellular signals regulating cell growth through the Hippo-dependent modulation of YAP/TAZ activity. When epithelial tissue organization is lost, such as in epithelial-to-mesenchymal transition (EMT) and tumorigenesis, these complexes lose their organization and YAP/TAZ are relocated into the nucleus [35–38]. In addition, **G protein-coupled receptors (GPCRs)** have been shown to regulate YAP/TAZ activity both through LATS1/2-dependent and -independent mechanisms [3].

Recently, a completely different mechanism has been described, taking place in the nucleus and linking mechanical cues to transcriptional regulation. Both YAP and TAZ interact in the nucleus with **switch/sucrose nonfermentable (SWI/SNF)** chromatin-remodeling complexes through the AT-rich interactive domain-containing protein 1A (ARID1A) subunit. This interaction is alternative to their binding to TEAD and results in YAP/TAZ inhibition. The SWI/SNF–YAP/TAZ complex is predominant under low mechanical stimulation, whereas in conditions of mechanical stress, F-actin accumulates into the nucleus and, binding to SWI/SNF, prevents the interaction of this complex with YAP/TAZ [39].

Finally, a reciprocal negative regulation of YAP and TAZ has also been reported as an established compensatory mechanism [40–43], although it has not been detected in every context [16].

Paralog-Specific Regulatory Mechanisms

Several studies have unveiled a complex and still controversial interplay between **WNT** and Hippo signaling, in which YAP and TAZ display not completely equivalent roles (Figure 3A). When WNT signaling is inactive, its nuclear transducer, **β-catenin**, is targeted for degradation by binding to a cytoplasmic destruction complex (DC), which consists of a scaffold protein, Axin1, and other factors, including adenomatous polyposis coli (APC), CK1, and GSK3. Phosphorylation of β-catenin by GSK3 primes it for ubiquitylation by β-TrCP and proteasomal degradation, preventing β-catenin accumulation and nuclear translocation. Conversely, the WNT ligand binding to Frizzled (FZD) transmembrane receptors induces the disassembly of the DC, allowing β-catenin nuclear accumulation and activation [3]. FZD receptors are the central transducers of WNT signaling, including both canonical and noncanonical WNT pathways. The noncanonical WNT signaling is independent from the DC and β-catenin and it antagonizes the canonical WNT pathway [44].

WNT signaling promotes YAP and TAZ nuclear localization and activity, although the mechanism is still controversial. Azzolin and collaborators showed that, in absence of WNT stimulation, YAP/TAZ interact with Axin1 and other components of the DC, with the consequence that both factors are sequestered into the cytoplasm [45]. Upon WNT ligand stimulation, YAP and TAZ are released from this complex, leading to WNT-activated YAP/TAZ-mediated transcriptional activation [3,45]. Park and collaborators showed that YAP and TAZ are activated by noncanonical WNT signaling through a β-catenin-independent mechanism, that involves G protein $G\alpha_{12/13}$ activation and LATS1/2-dependent regulation [44]. Conversely, activated YAP and TAZ inhibit canonical WNT signaling, although different mechanisms have been reported. The binding of YAP/TAZ to β-catenin or other WNT signaling components has been implicated in this inhibition [45–47], whereas in another work YAP/TAZ-dependent transcriptional activation of secreted WNT inhibitors was described [44].

Notably, it is widely reported that YAP nuclear localization and activity are increased by WNT signaling stimulation, whereas TAZ is also stabilized [25,44,45]. Although both β-catenin-dependent and -independent mechanisms have been proposed to justify TAZ stabilization, all of them are related to the presence of the second phosphodegron that is specific of TAZ, making it more unstable and susceptible to stability regulation than YAP (Figure 3A) [25]. In line with this concept, GSK3 kinase has been shown to phosphorylate TAZ on S58 and S62, which are not present on YAP, creating a binding site for β-TrCP. GSK3 is also a downstream member of the phosphoinositide 3-kinase (PI3K) pathway, being inhibited by PI3K signaling activation or *PTEN* mutations. Thus, PI3K pathway activation is another regulatory signaling event that stabilizes and activates TAZ through the GSK3 inhibition [23].

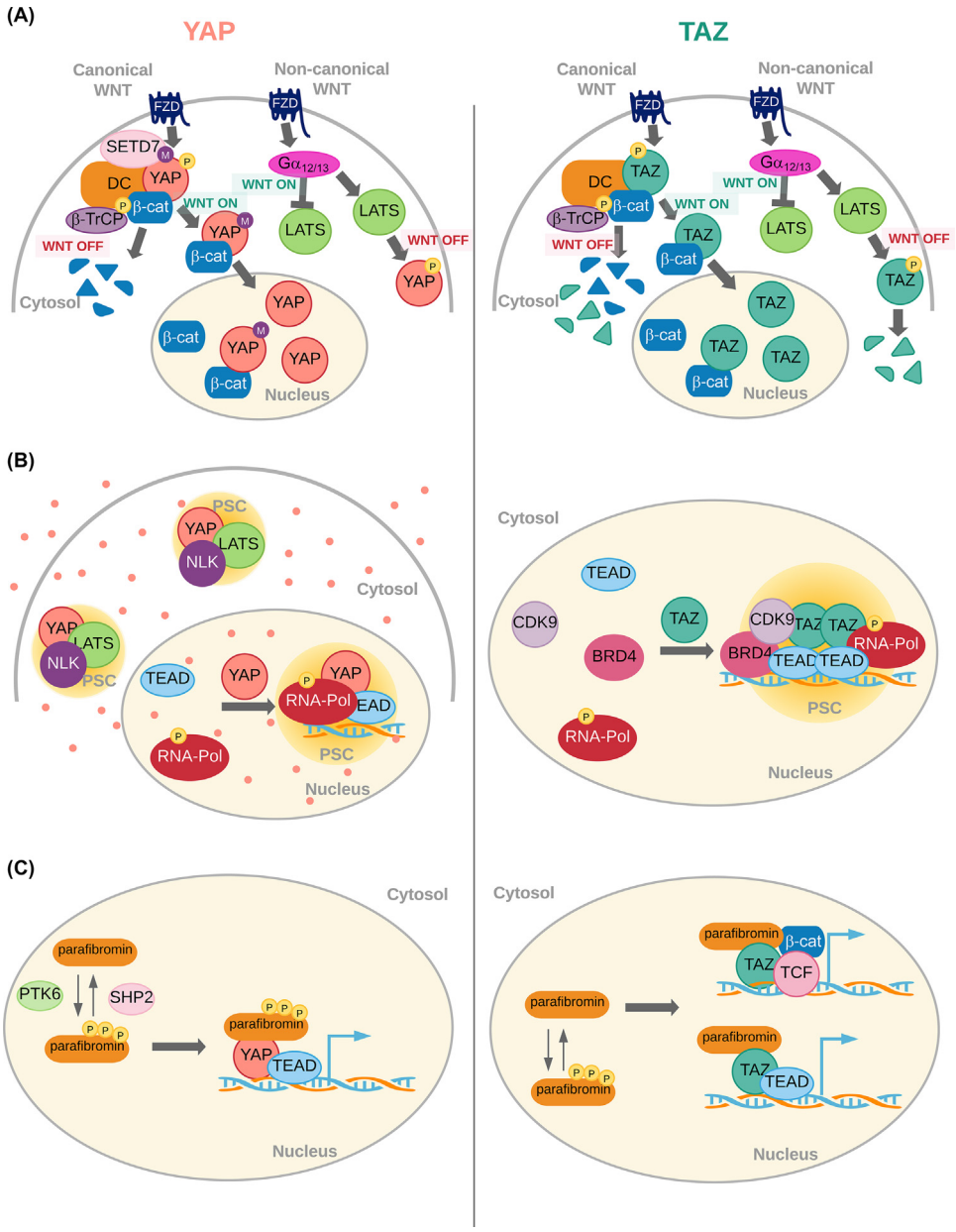

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Figure 3. Differential Regulatory Mechanisms of YAP and TAZ Activity. (A) Both YAP and TAZ interact with β-catenin and are part of the DC. Upon Hippo pathway activation, phosphorylated YAP and TAZ sequester β-catenin in the cytoplasm and promote its degradation, thus inhibiting the WNT signaling. WNT stimulation induces YAP and TAZ release from the DC and their translocation into the nucleus, activating the YAP/TAZ-mediated transcriptional response, in addition to the classical β-catenin/TCF-mediated transcriptional response. TAZ, but not YAP, is degraded upon interaction with the DC, through a phospho-β-catenin-dependent mechanism. Conversely, YAP, but not TAZ, methylation by SETD7 is crucial for its interaction with β-catenin. Nuclear localization and activity of both YAP and TAZ have been shown to be increased by WNT also through the noncanonical pathway in a $G\alpha_{12/13}$ and LATS1/2-dependent manner. In this context, TAZ is also stabilized by WNT. (B) Both YAP and TAZ hold the capacity to organize liquid-phase subcellular compartments. YAP promotes the formation of both cytoplasmic and nuclear compartments upon hyperosmotic stress stimulation, whereas TAZ promotes the formation of nuclear compartments also under unstimulated conditions. In both cases,

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As previously mentioned, YAP is the target of some post-translational modifications that are not reported for TAZ. Methylation on K494 by **SET domain containing 7 (SETD7)** is required for YAP cytoplasmic localization and, when impaired, induces its nuclear translocation, without influencing phosphorylation status and stability [30]. Further studies showed that SETD7-dependent methylation of YAP is also crucial for both YAP/β-catenin complex stabilization and β-catenin nuclear relocalization upon WNT stimulation (Figure 3A) [33].

YAP activity is also controlled by **p300/CBP** (p300 and CREB binding protein)-mediated acetylation and **silent mating type information regulation 2 homolog 1 (SIRT1)**-mediated deacetylation [34]. YAP deacetylation promotes its nuclear localization and the interaction with TEAD4, supporting transcriptional activity and cell growth [34]. Neither methylation nor acetylation has been reported for TAZ, although these modifications cannot be excluded, since they were not investigated in the works which characterized YAP modifications [30,33,34].

O-GlcNAcylation on YAP serine or threonine residues (S109 and T241) integrates the availability of metabolic nutrients, including glucose, glutamine, and acetyl-CoA, with the control of cellular processes [31,32]. This modification, which does not occur on TAZ, inhibits LATS binding and S127 phosphorylation and, conversely, promotes YAP stability and transcriptional activity. YAP O-GlcNAcylation is dependent on high glucose availability and may enhance YAP-dependent tumorigenesis, representing a crucial link between metabolism and cancer growth [31,32].

Another distinctive regulatory mechanism is the glucocorticoid-mediated stimulation of YAP activity. Glucocorticoid treatment induces fibronectin upregulation and cytoskeleton remodeling, leading to decreased LATS-dependent phosphorylation and increases YAP protein levels, nuclear localization, and transcriptional activity. The glucocorticoid–YAP axis supports breast cancer (BC) stemness and chemoresistance and may support a differential role of the two paralogs in BC [48].

Two recent studies unveiled the common ability of YAP and TAZ to localize into phase-separated condensates (PSCs) and to promote liquid–liquid phase separation, but through different mechanisms [49,50]. Subcellular compartmentalization by liquid–liquid phase separation has emerged as an essential process for transcription control, providing a framework in which gene expression is coordinately regulated. Notably, superenhancer-associated factors, such as **mediator of RNA polymerase II transcription subunit 1 (MED1)** and **bromodomain containing 4 (BRD4)** are main players of liquid–liquid phase separation [51]. Both YAP and TAZ hold the capacity to organize PSCs as transcriptional hubs, containing TEAD factors and components of the core transcription machinery, including RNA-Pol II, BRD4, MED1, and **cyclin-dependent kinase 9 (CDK9)**. TAZ has been shown to localize to PSCs under unstimulated conditions, whereas the presence of YAP in such structures has been observed only upon induction by

these phase-separated nuclear compartments are transcription control hubs, containing partner TEAD coactivators and core transcription machinery, including RNA-Pol II, BRD4, MED1, and CDK9. (C) Both YAP and TAZ interact and are stimulated by nuclear scaffold protein parafibromin. YAP-dependent transcription is activated by interaction with phosphorylated parafibromin, whereas transcriptional activity of TAZ and TAZ/β-catenin containing complexes is promoted by unphosphorylated parafibromin. Thus parafibromin phosphorylation status, regulated by SHP2 phosphatase and PTK6 kinase, dictates mutually exclusive YAP or TAZ activation. Abbreviations: β-cat, β-catenin; BRD4, bromodomain containing 4; CDK9, cyclin-dependent kinase 9; DC, destruction complex; FZD, Frizzled; LATS1/2, large tumor suppressor kinase 1 and 2; MED1, mediator of RNA polymerase II transcription subunit 1; NLK, nemo like kinase; PSC, phase-separated compartment; RNA-Pol, RNA polymerase; SETD7, SET domain containing 7; TAZ, WW domain containing transcription regulator 1; TEAD, TEA domain; β-TrCP, β;-transducin repeat containing E3 ubiquitin protein ligase; WNT, wingless-type MMTV integration site; YAP, Yes-associated protein.

hyperosmotic stress (Figure 3B). YAP-mediated phase separation requires the C-terminal transactivation domain, whereas TAZ-dependent compartmentalization requires the WW domain and even more the coil-coiled domain [49,50]. Intriguingly, TAZ, but not YAP, holds the ability to homodimerize through this coiled-coil domain, leading to the hypothesis that homodimerization may determine differences in phase compartmentalization (Figure 3B) [50].

A particularly elegant mechanism of differential regulation of YAP and TAZ has been recently described for parafibromin, a nuclear scaffold protein which is a common interactor (Figure 3C). YAP interacts with both the dephosphorylated and phosphorylated forms of parafibromin, whereas TAZ specifically forms a complex with only the dephosphorylated form. Dephosphorylated parafibromin stimulates the transcriptional activity of TAZ and β-catenin/TAZ complex. On the contrary, only phosphorylated parafibromin increases YAP activity. These findings unveil a mechanism leading to mutually exclusive YAP and TAZ activation, depending on parafibromin phosphorylation balance [52].

Distinct Partners Regulate Distinct Transcriptional Programs

Differences in structural features of YAP and TAZ can lead to interactions with distinct transcriptional partners, which dictate the binding to specific regulatory regions. Indeed, interactome studies confirmed that YAP and TAZ have both common and specific interactors [53,54].

Common YAP and TAZ Transcriptional Partners

Beside TEAD proteins, many other transcription factors cooperate with YAP and TAZ to promote specific programs during physiological development and/or cancer progression, including RUNX1/2 [55–57], paired box gene 3 (PAX3) [58,59], T-box transcription factor 5 (TBX5) [17,28], and AP-1 [60] (Table 1). In addition, YAP and TAZ associate with BRD4, a chromatin general regulator and histone acetylation reader. YAP/TAZ specifically localize at genomic regions with superenhancer features, in which they promote BRD4 and RNA-Pol II binding [61].

A peculiar connection links YAP and TAZ to the SMAD (small mother against decapentaplegic) family of transcription factors. SMAD proteins transduce signals from transforming growth factor (TGF)β and bone morphogenetic protein (BMP), being SMAD2/3 activated from the former and

Table 1. YAP and TAZ Transcriptional Partners

Partner	Interaction domain	Function	YAP/TAZ	Refs
TEAD1–4	TEAD binding domain	Promoting transcription	YAP, TAZ	[97]
RUNX1/2	WW	Promoting transcription	YAP, TAZ	[55–57]
PAX3	WW	Promoting transcription	YAP, TAZ	[58,59]
TBX5		Promoting transcription	YAP, TAZ	[17,28]
AP-1		Promoting transcription	YAP, TAZ	[60]
SMAD2–4	CC	Nuclear shuttling; promoting transcription	YAP, TAZ	[38,62]
SMAD1	WW	Promoting transcription	YAP	[67]
SMAD7	WW	Promoting inhibitory function	YAP	[68]
p73	WW	Promoting transcription	YAP	[70–72]
ERBB4	WW	Promoting transcription	YAP	[74,75]
PPARγ	WW	Suppressing transcription	TAZ	[56]
NFATC5	pY316	Suppressing transcription	TAZ	[26]
STAT1	STAT1 binding motif	Inhibiting STAT1/2 dimerization	YAP, TAZ	[21]

SMAD1 from the latter. Upon activation, both SMAD2/3 and SMAD1 interact with SMAD4 co-regulator and translocate into the nucleus, whereas SMAD7 is an inhibitory member of the family. Both YAP and TAZ have been shown to associate with heteromeric SMAD2–4, regulating their subcellular localization [38,62]. Indeed, YAP and TAZ are often associated with SMADs in the same transcriptional complexes, regulating common target genes [63,64]. Furthermore, TAZ, but not YAP, is induced upon TGFβ treatment, adding a further layer of regulation [64–66].

Conversely, YAP, but not TAZ, interacts with SMAD1, resulting in a transcriptional response to BMP signaling [67]. Finally, YAP has been reported to be an interactor of SMAD7, potentiating its inhibitory activity (Table 1) [68].

TAZ-Specific Transcriptional Partners

TAZ specifically binds peroxisome proliferator-activated receptor (PPARγ), a member of the nuclear hormone receptor superfamily, which is critical to adipocyte differentiation. Notably, TAZ inhibits the ability of PPARγ to stimulate gene expression in both presence and absence of the PPARγ-activating ligand, thus acting as a transcriptional co-repressor in the context of adipogenesis. In the same study, TAZ is described as coactivator of RUNX2 in stimulating osteogenic differentiation (Table 1). These results indicate a crucial role for TAZ in fate decision during mesenchymal stem cells development (Box 1) [56].

TAZ has a crucial role in kidney development and homeostasis (Box 1) [10,11]. In the context of renal medullary cells, TAZ is phosphorylated on Y316 by c-Abl kinase upon hyperosmotic stress. Y316 phosphorylation induces TAZ binding to NFATC5, a transcription factor regulating kidney hyperosmotic stress response (Table 1). Interaction between phospho-TAZ and NFATC5 suppresses the NFATC5-dependent transcription program, unveiling a mechanism of hyperosmotic stress-dependent regulation of gene expression and TAZ as a transcriptional repressor [26].

YAP-Specific Transcriptional Partners

Several studies have reported an unusual tumor suppressor function of YAP, mediated by its ability to bind p73 (Table 1 and Box 2). p73 is a transcription factor belonging to the p53 family that induces apoptosis, growth arrest, and differentiation [69]. YAP interacts with p73 through its WW domain and the PPxY motif of p73. This interaction results in enhanced p73 transcriptional activity and cell apoptosis in response to DNA damage [70–72]. Notably, forced YAP activation in hematological cancers triggers apoptosis, further supporting its role as tumor suppressor [73].

Another YAP specific interactor is the erb-b2 receptor tyrosine kinase 4 (ERBB4) receptor (Table 1). ERBB4 is a tyrosine kinase receptor of the epidermal growth factor receptor (EGFR) family, whose intracellular domain is cleaved upon neuregulin ligand binding and relocates into the nucleus. Proteolytic cleavage induces relocalization of ERBB4 cytoplasmic domain into the nucleus where it can act as transcription factor, directly inducing target genes. YAP and ERBB4 have been shown to interact through the WW domain of YAP and the PPxY motif of ERBB4. This interaction stimulates transcription of both ERRB4 and YAP target genes, providing a direct link between YAP and EGFR signaling [74,75].

YAP and TAZ Control Distinct Transcriptional Programs

We have highlighted remarkable differences in YAP/TAZ structure, post-translational modifications, regulatory mechanisms, and interactors. It is reasonable that these discrepancies lead to activation of transcriptional programs that are not completely overlapping. Indeed, several works analyzed the single KO of YAP or TAZ, uncovering both common and distinctive transcription targets [7,8,50]. In HEK293 cells it was shown that the silencing of YAP had a greater impact in regulating

cell spreading, volume, and granularity [7]. Moreover, the loss of YAP impaired glucose cell uptake, which was not affected by TAZ, and induced a significant arrest in cell proliferation. YAP and TAZ functional divergency was associated with different transcriptional programs, since the deletion of YAP displayed a stronger down-regulation of connective tissue growth factor and cysteine-rich angiogenic inducer 61 (CYR61) expression, whereas other standard YAP/TAZ-targeted genes, including *AMOTL2* and *FOSL1*, were under the transcriptional control of YAP only [7].

In non-small-cell lung cancer cell lines, an even more striking division of roles for YAP and TAZ has been described. In this setting, YAP mostly controls genes related to cell division and cell cycle progression, whereas TAZ preferentially regulates genes associated to ECM organization and adhesion. Accordingly, YAP is sufficient to promote cell cycle progression, whereas TAZ activity is determinant in enhancing cell migration [8].

Notably, the YAP/TAZ relative contribution to control cell functions in physiology and disease are reported to be largely context dependent (Boxes 1 and 2).

Concluding Remarks

Although mostly considered as functionally redundant, increasing evidence supports the existence of differential roles of YAP and TAZ in many contexts, from organ morphogenesis and tissue homeostasis to cancer development and progression (Boxes 1 and 2) [9,10,76]. These distinctive functions likely rely on protein structure differences, differential expression, specific regulatory mechanisms, and distinct interacting partners [16,31,50].

The differential functions of YAP and TAZ have been largely underestimated. Future studies should assess the individual contributions of YAP and TAZ. This may be particularly important for mechanistic and translational studies that aim to exploit YAP and TAZ as anticancer therapeutic targets and/or disease biomarkers (see Outstanding Questions).

Outstanding Questions

Which YAP and TAZ molecular features support their context-specific functions?

Which transcriptional programs are solely under the control of YAP and which ones are specifically regulated by TAZ, supporting their distinctive biological functions?

What is the contribution of YAP and TAZ reciprocal compensatory regulation to target genes expression and cell phenotype?

What is the relative contribution of YAP and TAZ to physiological organ development and to cancer onset and progression?

What is the relevance of YAP/TAZ-specific regulatory mechanisms in modulating development and malignancies?

What is the extent and which are the molecular bases of YAP and TAZ opposing roles in regulating physiological development and cancer progression?

YAP and TAZ are frequently identified as interchangeable targets in anticancer therapies. However, is it always advantageous to inhibit both of them, considering their distinct and specific features?

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