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YAP/TAZ as master regulators in cancer – modulation, function and therapeutic approaches

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Abstract

Our understanding of the function of the transcriptional regulators YAP/TAZ in cancer is advancing. In this Review, we provide an update on recent progress in YAP/TAZ biology, their regulation by Hippo signaling and mechanotransduction, and highlight open questions. YAP/TAZ signaling is an addiction shared by multiple tumor types and their microenvironments, providing many malignant attributes. As such, it represents an important vulnerability that may offer a broad window of therapeutic efficacy, and here we give an overview of the current treatment strategies and pioneering clinical trials.

Multiple solid malignancies display accumulation and activation of YAP/TAZ, paralogous genes encoding for transcriptional co-activators related to *Drosophila* Yorkie. Their activation positively correlates with malignancy, relapse, metastasis, lower overall survival and chemoresistance. Genetic evidence in mouse models and human cancer cells reveals that YAP/TAZ activity is essential for tumor initiation and progression (Table 1). These studies suggest that YAP/TAZ may represent master transcriptional regulators of cancer and their engagement by cancer cells may serve as an epigenetic "switch" to enable phenotypic plasticity, a fluid cell state essential to adapt to nutrient deprivation, escape immune attack, and resist stresses associated with the metastatic cascade. Accumulating evidence implies that YAP/TAZ also act as a nexus by which tumor cells can reprogram their surrounding ecosystem, including fibroblasts, immune and endothelial cells, into a resilient, growth-promoting and immunologically cold tumor microenvironment (TME). As such, YAP/TAZ are appealing candidates as orchestrators of “tumor morphogenesis” by acting on the tumor's epithelial and stromal components.

YAP/TAZ as transcriptional determinants

YAP and TAZ do not bind DNA directly but require DNA-binding partners in order to associate to cognate cis-regulatory elements on chromatin. In the large majority of normal

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and cancer cells, these partners are the TEAD family members (reviewed in Ref. 1). The YAP/TAZ-TEAD complexes are mainly recruited to enhancer elements, and, in a minority of cases, to promoters[1] (Figure 1a). These regulatory elements are typically co-bound by AP-1 transcriptional complexes (heterodimers of FOS and JUN family members), which are required for the transcriptional activation of a relevant portion of YAP/TAZ target genes[1]. YAP/TAZ promote the recruitment of general transcriptional coactivators, such as MED1, BRD4 and CDK9, to enhancers (Figure 1a). This induces the formation of liquid-liquid phase separated bodies, essential for transcriptional responses[1]. Once bound to enhancers, YAP/TAZ induces the recruitment of RNA polymerase II (POLII) at the promoters of YAP/TAZ target genes, at least in part by favouring the recruitment of BRD4 at the same loci. In fact, YAP/TAZ dictate the genome-wide association of BRD4 to chromatin, endowing YAP/TAZ-bound enhancers the same functional properties of superenhancers[2]. In addition, recent evidence indicates that YAP/TAZ can feed their own transcriptional responses by Tet1-mediated rewiring of TEAD-responsive enhancers[3].

Regulation of YAP/TAZ by the Hippo pathway

The Hippo pathway is a cascade composed of two kinases, that is MST1/2 and LATS1/2, and of their respective cofactors, Sav1 and Mob1A/B[4] (Figure 1b). Other components of the Hippo pathway include the adaptor protein NF2, and the MAP4K4 family and the PTPN14 phosphatase. MST1/2 or MAP4K4 phosphorylate and activate LATS1/2, which in turn phosphorylate YAP/TAZ; this is considered an inhibitory step promoting YAP/TAZ cytoplasmic sequestration and protein degradation[4]. Yet, to what extent the direct phosphorylation of YAP/TAZ by LATS1/2 is relevant for their inhibition at endogenous protein levels and in vivo still awaits genetic validation[5].

As shown in Table 2, some human tumor types display genetic alterations in components of the Hippo pathway (reviewed in Ref. 4). This includes NF2 mutations or deletions in mesotheliomas, medulloblastomas and schwannomas; NF2 and LATS1/2 mutations in renal cell carcinomas; and Sav deletions in cholangiocarcinomas. These genetic alterations occur at various frequencies and despite consistently elevated YAP/TAZ activation, even in these tumors types genetic alterations are absent in the majority of cases. For all other tumors, in spite of pervasive and widespread YAP/TAZ hyperactivation, genetic loss of the Hippo pathway is either extremely rare or non-existing; and, irrespectively of genetics, there is actually scant evidence of changes in the level of active, phosphorylated LATS1/2 in tumors compared to normal tissues. Thus, YAP/TAZ activity is induced in human tumors without requiring the inactivation of Hippo pathway components. Of note, even in mouse models, loss of Hippo pathway components is either inconsequential or insufficient for tumor formation in several adult tissues, such as intestine, mammary gland, pancreas, lung, and skin[6–11]. And yet, tumors induced by transgenic oncogenes in these same tissues display elevated YAP/TAZ activity and require YAP/TAZ for their emergence.

Why are Hippo pathway mutations so rare in epithelial tumors? A plausible answer to this riddle is that mutations in the Hippo pathway may be in fact detrimental for cancer cells. This could entail Hippo-dependent, but YAP/TAZ-independent regulation, including the requirement of LATS1/2 as checkpoints of anti-tumor immunity[12], as regulators of mitotic

stress through phosphorylation of Aurora B kinase, or in the context of lipid metabolism and epigenetics[13,14].

Regulation of YAP/TAZ by mechanotransduction

YAP/TAZ are overarchingly regulated by mechanotransduction, a tissue-level informational system based on the exchange of physical forces between cells and their extracellular matrix (ECM)[15,16]. Via mechanical signals cells are informed of perturbations of their surroundings, and of their own shape, polarity and cytoskeletal organization. Mechanical forces in living tissues are the product of local patterns of geometrical and mechanical strains, which are related to the positioning of the cell within the 3D tissue architecture and to the composition of the stromal milieu[16,17]. Mechanical signals are generated by the interplay between cell-generated traction forces and resisting forces within the ECM. Integrins are key mediators of such interplay, connecting, on their cytoplasmic side, with the F-actin cytoskeleton through Focal Adhesions, in a manner involving the ILK, FAK and Src proteins[18] (Figure 1b). As response to extracellular forces, the cell increases F-actin contractility and restructures its entire cytoskeleton in a process requiring Rho-GTPases (such as Rho or Rac1), myosin activity and ROCK[19]. This Integrin/FA/Rho-Rac/ROCK/F-actin core mechanosignaling engine is also an appealing target of therapeutic interventions, as discussed at the end of this review.

A missing link in the field is how to connect the F-actin architecture of mechanically activated cells with YAP/TAZ nuclear localization and activation (Figure 1b). A key permissive step in YAP/TAZ nuclear entry is the opening of the nuclear pores by nucleo-cytoskeletal coupling[20]. In addition, mechanosignaling also enhances YAP/TAZ transcriptional responses by releasing their association with components of the SWI/SNF complex[21] (Figure 1a). Besides these regulations, how mechanically modulated F-actin in the cytoplasm controls YAP/TAZ nuclear entry remains a matter of speculation; for example, cytoplasmic F-actin may trap or promote degradation of sequestering factor(s) that prevent YAP/TAZ nuclear accrual.

In addition, LATS1/2 have been proposed as elements by which mechanically modulated F-actin regulates YAP/TAZ[22–24]. However, if LATS1/2 were downstream of F-actin, then LATS1/2 activity, as measured by LATS phosphorylation, should be patterned by mechanotransduction. In contrast, there is limited evidence of such modulation. Moreover, if cell mechanics were upstream of LATS1/2, cells depleted of LATS1/2 should be insensitive to mechano-modulations. In contrast, LATS1/2 inactivation can hardly rescue YAP/TAZ function when mechanosignaling is overtly inhibited[15,20,25–34]; intriguingly, LATS1/2 in fact requires at least some residual F-actin cytoskeleton in order to blunt YAP/TAZ activity[32]. Our interpretation of these data is that LATS1/2 represent a tonic checkpoint that is formally dispensable for the F-actin/YAP/TAZ axis, but that remains relevant for inhibition of such axis. Of note, LATS kinases have been shown to regulate components of the F-actin regulatory machinery, such as ENA and AMOT[35–39] and these, in principle, may represent effective means by which LATS could interfere with YAP/TAZ activity, although indirectly, through the cytoskeleton (Figure 1b). Changes in YAP phosphorylation at LATS1/2 sites are consistently detected upon modulation of mechanosignaling[4]. However, it should be noted

that such phosphorylation does not automatically imply a direct involvement of LATS1/2 in YAP/TAZ mechanotransduction, as this may represent a reinforcing step, secondary to any YAP/TAZ inhibitory mechanism that leads to YAP/TAZ cytoplasmic accumulation (where LATS1/2 mainly operate). A conservative interpretation of these results is that YAP/TAZ protumorigenic effects requires sufficient mechanosignaling and concomitant attenuation of Hippo kinase activity. To conclude, a truly comprehensive molecular understanding of the link between mechanosignaling and YAP/TAZ regulation is still lacking.

Nevertheless, if inactivation of the Hippo pathway is an unlikely culprit for the widespread YAP/TAZ hyperactivation in solid tumors, the question of whether mechanosignaling serves such a purpose emerges. Addressing this question remains a major quest in cancer biology. Recent evidence suggests that normal tissue architecture is a potent tumor suppressor that keeps YAP/TAZ at bay by opposing their nuclear accumulation[16,24,27,34,40]. Indeed, during injury and regeneration (in skin, pancreas, lung, heart, intestine and liver), cells react to mechanical changes in their surrounding by activating YAP/TAZ and initiating a highly choreographed cellular and supracellular program that drives tissue healing back to homeostatic mechanical equilibrium until the wound is resolved and YAP/TAZ inactivated (reviewed in 41–43). In contrast, tumors are “chronic wounds”, tissues with distorted architecture that never resolves, characterized by increased ECM deposition and stiffness, inflammation, edema, and altered vascular blood flow[44]. These environmental changes may profoundly affect the mechanics, contributing to persistent YAP/TAZ activation[16,24,27,34,40] (Figure 2).

In addition to extrinsic mechanical cues, recent mechanistic inspections revealed that mechanosignaling contributes to YAP/TAZ activation in cancer also downstream of key oncogenes, soluble factors, and GPCR signaling, as described in the following section.

Regulation of YAP/TAZ by oncogenic alterations

In the following sections we will discuss in detail how YAP/TAZ are regulated by oncogenic alterations that aberrantly activate intracellular signaling.

GPCR signaling

A number of growth factors operate through G-protein-coupled receptors (GPCRs), in turn either inducing or suppressing YAP/TAZ activity[23]. This suggests that oncogenic mutations in G-protein α-subunits in different types of cancer may in fact work by promoting YAP/TAZ activity. A case in point is uveal melanoma, where gain-of-function mutations of Gαq (occurring in 90% of cases) drive tumor growth in vivo. Prerequisite for this regulation is a sufficient induction of Integrin/FAK mechanosignaling[26,45]; GPCR signaling in uveal melanoma entails both LATS-independent rewiring of the actin cytoskeleton through Rho (Figure 2), but also MOB phosphorylation and LATS inhibition[26,45,46]. Intriguingly, recent work found that tissue-specific oncogenic GPCR ligands can be secreted by stromal cells to promote YAP activity in epithelial cells. A prominent example is prostaglandin E2 secreted by intestinal mesenchymal cells, that signals through the GPCR Ptger4 expressed in epithelial cells, causing YAP nuclear accumulation and hyperactivation[47].

RTK/RAS/RAC1 signaling

A main oncogenic driver contributing to YAP/TAZ activity is receptor tyrosine kinase (RTK)-Ras signaling[27,34]. Oncogenic mutations in RTK signaling, such as those affecting K-Ras or Erbb2, indeed change cellular mechanosensing by increasing F-actin stress fibers and contractility through their downstream effector Rac1[27] (Figure 2). This sensitizes epithelial cells to increases in ECM stiffness akin those measured in tumors. In doing so, oncogenes become integral to mechanotransduction and exploit YAP/TAZ to drive cell fate reprogramming and transformation[27]. In metastatic colorectal cancer (CRC), blockade of hyperactive EGFR reduces YAP activity and tumor growth[48]. Notably, YAP/TAZ regulation through cytoskeletal remodeling might also incorporate the effects of other oncogenic lesions. For instance, Src has been reported to be upstream of YAP/TAZ[30]; then mutant-p53 has been recently linked to the activation of Rho/Rac1/ROCK, as such impacting cell mechanics and YAP/TAZ[30,34,49]. Downstream of oncogenic RTK signaling, YAP/TAZ activity accounts for a large fraction of oncogene-induced transcriptional responses[27].

In spite of oncogenic RTK/Ras/Rac1 being able to boost mechanosignaling, the normal compliance of healthy epithelial layers is far below the threshold required to turn on YAP/TAZ mechanotransduction (Figure 2); in these conditions, oncogene-bearing cells do not transform and remain functionally and transcriptionally indistinguishable from their normal counterparts[27,50]. It is tempting to speculate that this phenomenon may account for the observation in genome sequencing data that ostensibly healthy human tissues can display the same type and number of oncogenic mutations found in malignancies of the same tissue[51–53].

SWI/SNF

Inactivation of components of the nuclear SWI/SNF complex, and in particular of ARID1A, occurs at very high frequencies in a variety of human malignancies[54]. ARID1a binds and inhibits YAP/TAZ in the nucleus, anchoring them to the BAF-SWI/SNF complex. This nuclear buffering of YAP/TAZ activity is also dependent on the tensional state of the cells, as the BAF-SWI/SNF complex preferentially binds nuclear F-Actin in conditions of elevated mechanical strain, leading to release of nuclear YAP/TAZ from ARID1a inhibition[21] (Figure 1a). Thus, increased mechanical stimulation does not only promote YAP/TAZ nuclear entry, but also contributes to relieving nuclear inhibitors. Intriguingly, it has recently been reported that treatment of triple negative breast cancer (TNBC) cells with FGFR inhibitors can suppress the function of the SWI/SNF complex, enabling YAP/TAZ recruitment to cognate enhancers and expression of YAP/TAZ-driven therapy resistance genes[55].

Epithelial-to-mesenchymal transition (EMT) and cell polarity

EMT has been associated with increased cancer malignancy and stemness[56] and its activation by Twist or Snail precedes TAZ activation and stemness induction by disrupting the localization of the epithelial polarity factor Scribble[57]. In turn, Scribble is also controlled by the oncosuppressor LKB1, and loss of LKB1 favors emergence of non-small cell lung cancer in a YAP/TAZ-driven manner[58,59]. Inactivation of FAT1, a protocadherin frequently mutated in human cancers[60], promotes malignant skin squamous carcinomas (SCCs) in mouse models in part by installing a hybrid EMT[61]. This process involves CAMK2/CD44/

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Src-mediated activation of YAP/TAZ mechanotransduction and FAT1-knockout tumor cells behave on soft substrates as if they were exposed to a stiff ECM[61]. Of note, FAT1 truncating mutations have been identified in head and neck SCCs as the top genetic alterations associated with increased YAP/TAZ activity[60].

Wnt signaling

YAP and TAZ can bind to components of the β-catenin destruction complex Axin, APC and β-catenin itself[62–64]. This configures a crosstalk between YAP/TAZ, Hippo and Wnt signaling, such that cytoplasmic YAP/TAZ (in a Hippo ON scenario) can inhibit Wnt stimulation[62,64–66]. Conversely, Wnt can lead, at least in certain cellular contexts, to the activation of YAP/TAZ, either through canonical inhibition of the destruction complex or through non-canonical Wnt signaling. For example, strong accumulation of nuclear YAP/TAZ has been reported in Wnt1-induced mammary tumors[67,68], and in APC-mutant intestinal epithelium, where YAP/TAZ are required for APC-driven transformation[62,63,69,70].

Viral oncogenes

YAP/TAZ activation also occurs downstream of oncogenic viral infection. This is the case for cervical carcinoma driven by Human papilloma virus, whose E6 and E7 oncogenes can promote YAP protein stabilization through a compiled mechanism involving Scribble inhibition and regulation of cytoskeletal dynamics[71–73]. Another example is Kaposi sarcoma-associated herpesvirus, triggering YAP/TAZ activation through Gαq/11 and Gα12/13[74].

Regulation of YAP/TAZ by alteration of their coding-genes

The most common genetic alterations targeting YAP/TAZ-coding genes (*YAP1* and *WWTR1*, respectively) in cancer are amplifications, mostly occurring in a fraction of squamous cell carcinomas (cervical, head and neck and esophageal SCCs) and in ovarian cancers[75] (Table 2).

Other genetic alterations targeting YAP/TAZ in cancer are gene fusions. These events occur at high frequency only in rare tumor types (Table 2)[76]. The chimeric proteins generated by these fusions invariably contain the TEAD-binding domain of YAP or TAZ, combined with a new C-terminal portion derived from a different transcription factor (Table2 for specifics) containing a nuclear localization signal and a transcriptional activation domain. As result, these fusion proteins accumulate in the nucleus, and promote the transcription of YAP/TAZ target genes[77–79]. A case in point is YAP/TAZ oncogenic fusions that cause epithelioid hemangioendothelioma (EHE). This monogenic tumor type may benefit from anti-YAP/TAZ therapy, in analogy to other monogenic tumor types (e.g., BCR-Abl-driven cancers). Of note, simvastatin, inhibiting Rho-GTPases and YAP/TAZ mechanosignaling, had dramatic inhibitory effects on endothelial cells transformed by TAZ-CAMTA1 fusion oncogene[78]. It is also worth discussing that YAP, but not TAZ, display several splicing variants, with some short isoforms of YAP1 being able to form heterodimers with TAZ endowing specific transcriptional responses[80,81].

YAP/TAZ as tumor suppressors

In contrast to the widespread activation of YAP/TAZ in the vast majority of solid tumors (YAP/TAZ^{ON}-type), the opposite behavior, with inhibited YAP/TAZ (YAP/TAZ^{OFF}-type), has been detected in hematological malignancies[82]. Myelomas, Lymphomas, and Leukemias display very low transcriptional expression of YAP and TAZ mRNAs[82–84], which, at least in part, is related to focal deletion of *YAP1* in a fraction of these tumors[83,84]. Survival analyses indicate that residual YAP expression is prognostic of better survival for patients with Multiple Myeloma or Acute Myeloid Leukemia (AML)[83,84], suggesting a tumor suppressive role for YAP in these contexts. Supporting this notion, YAP reconstitution dampens cell proliferation and induces cell death in human Multiple Myeloma and AML cells[83].

Solid tumors displaying very low YAP/TAZ protein expression and transcriptional activity have also been reported; intriguingly, these are cases carrying genetic inactivation of the *Rb* locus and displaying molecular traits related either to neural cells (e.g., Retinoblastoma), or to neuroendocrine cells (e.g., Small Cell Lung Cancer (SCLC))[82]. Functionally, forced YAP/TAZ activation induces growth arrest and apoptosis in cell lines originated from these tumors and genetic inactivation of YAP/TAZ promotes tumor growth and progression, and reduces survival in mouse models[82], indicating that YAP/TAZ act as tumor suppressors. Mechanistically, YAP/TAZ^{OFF}-type of tumors appear to be characterized by a peculiar set of TEAD-bound enhancers; contrasting YAP/TAZ^{ON} tumors, which are void of AP1 cooperating elements[82], at least suggesting the potential involvement of other TEAD partners with tumor suppressive functions.

Hallmarks of YAP/TAZ activity in cancer

Once the above-described regulations raise nuclear YAP/TAZ accumulation above a critical threshold, the gene expression programs induced by these factors empower a number of fundamental attributes in cancer cells[85]. These include phenotypic plasticity, drug resistance, cell proliferation, and gain of metastatic abilities; other attributes represent non-cell autonomous mechanisms, including the control of stromal cells, inflammation, senescence, immunity, angiogenesis and cell competition, some of which have been described as “enablers” of the cancer phenotype[85].

Cancer cell plasticity

Exogenous expression of YAP or TAZ in healthy, differentiated cells, is sufficient to convert them into cells operationally and molecularly resembling tissue-specific stem cells (SCs)[86]. Similarly, overexpression of TAZ can convert non-stem tumor cells into cancer stem cells (CSCs)[57] (Figure 3a). These findings, while highlighting the potent epigenetic effects of YAP/TAZ, also raise questions as to when YAP/TAZ-mediated cell fate reprogramming becomes important in living tissues. YAP/TAZ are in fact dispensable in healthy, adult epithelia, including normal SCs, but essential for tissue regeneration, tumorigenesis and ex vivo growth as organoids[6,27,31,41–43,62,87–93]. Thus, SC-like cells induced by YAP/TAZ under regenerative/tumorigenic conditions are different from normal SCs that do not rely on YAP/TAZ. Collective work in the intestine started to shed light on these questions: during intestinal regeneration, YAP/TAZ are key to generate, even from residual differentiated cells,

progenitor cells that are in fact very special. These regenerating SCs indeed display traits typical of the fetal intestine, bearing no resemblance with any of the cell types of the adult (including adult SCs)[69,92–95]. It is thus temping to speculate, given the parallel requirement of YAP/TAZ for tumor emergence, that these special progenitor cells may also represent the cancer cell of origin, generated through YAP/TAZ-mediated reprogramming of normal, differentiated cells (Figure 3a). Although this hypothesis remains to be functionally tested, it should be noted that YAP/TAZ-driven cell fate reprogramming has been observed in different cellular contexts, in mammary luminal cells, astrocytes, hepatocytes, pancreatic acinar cells and Schwann cells[86,96–101], that is in cells that also correspond to the tumor cell of origin in their corresponding tissues. This at least suggests the potential for a general involvement of YAP/TAZ-mediated reprogramming in tumor initiation.

Consistent with the ability of YAP/TAZ to favor progenitor cell states, recent single cell analyses of glioblastoma multiforme (GBM) also showed that YAP/TAZ sit at the apex of a gene-regulatory networks that maintains plasticity and aggressiveness of GBM cells[101]. Blocked differentiation by YAP/TAZ would also be consistent with the association of YAP/TAZ activation with less differentiated and more aggressive tumor types, including breast cancer, colon cancer, lung squamous cell carcinoma, pancreatic cancer, CRC, head and neck squamous cell carcinoma and osteosarcoma[42] (Table 1).

Cell proliferation

Enhancing cellular proliferation is a well characterized effect of YAP/TAZ activation, at least in vitro. As reviewed elsewhere[42,102], in cancer cell lines, YAP/TAZ sustain proliferation by direct transcriptional induction of a number of mitotic and DNA replication factors, promotion of the cell cycle, and by sustaining expression of oncogenic transcription factors, such as AP1 (in turn feeding on YAP/TAZ-transcription) or, depending on the cell type, c-Myc[91,103–105]. It is worth noting that enhancing cell proliferation is an element of YAP/TAZ-induced stemness that may only be induced in presence of other cooperating transcription factors and contextual signals[91]. For example, YAP/TAZ inactivation in glioma affects stemness properties, yet cell proliferation is only affected indirectly[101].

Drug resistance

Induction of phenotypic plasticity by YAP/TAZ also ensures adaptability to stressful conditions and/or adoption of quiescent fates that enable cancer cells to escape therapeutic treatments (Figure 3b). YAP/TAZ can promote resistance to both cytotoxic (e.g. paclitaxel, doxorubicin, cisplatin, UV, radiation) and targeted therapies (RAF, MEK, ER, CDK4/6 and Erbb2 inhibitors) in diverse tumor types[55,57,106–116] and also controls entry and exit of tumor cells from therapy-induced dormancy, as observed in non-small cell lung cancer after treatment with EGFR inhibitors[117,118], or in CRC after chemotherapy[119]. Intriguingly, in the latter case, disease relapse is promoted by chemotherapy-induced FAK-dependent YAP activation, involving a restructuring of cell-ECM adhesion and, likely, of the cytoskeleton[119]. Additionally, YAP/TAZ have been recently proposed to drive resistance to the multi-kinase inhibitor Sorafenib in liver cancer by preventing Sorafenib-induced ferroptosis[120].

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Activation of YAP/TAZ after pharmacological inhibition of driving oncogenes has been connected to increased mechanotransduction in resistant cells. This is the case for vemurafenib-resistant BRAF-mutant melanoma cells[112] and lapatinib-resistant HER-2 positive breast cancer cells[113]. These results are compatible with the view that ECM remodeling and changes in tissue stiffness may activate mechanosensing pathways promoting YAP/TAZ activation after these treatments were initially successful in tumor control. This may further imply that a combinatorial therapeutic strategy that combines oncogene-specific targeted therapy with inhibition of mechanotransduction might be a powerful means to overcome resistance mechanisms.

Metastasis

During metastasis, malignant cells must withstand a stressful journey, escape immune surveillance and co-opt local and systemic factors for recurrence after therapy. Our molecular understanding of these processes, and of their interconnections, remains limited. Intriguingly, experimental gain-of-YAP/TAZ is sufficient to provide full metastatic potential to non-metastatic cells, from dissemination to organ colonization, while YAP/TAZ inactivation impedes metastasis (reviewed in Ref. 121). The available evidence indicates that YAP/TAZ contribute to distinct aspects of the metastatic cascade (Figure 3c). To start, YAP/TAZ activity can foster metastatic dissemination through cell migration and invasion[61,122–126], survival in the circulation[127] and endothelial transmigration[128–130]. Disseminated cells can spread in a pericyte-like behavior through L1CAM-medited adhesion to vessel walls in the host tissue; such spreading mechanically activates YAP/TAZ that awaken metastatic cells form dormancy[131]. These YAP/TAZ-regulated processes may represent special attributes, acquired *de novo* and distinct from those establishing malignancy at the primary tumor site; or alternatively, may be additional adaptations of the same YAP/TAZ-orchestrated cell plasticity program at play in primary tumors. More work is required to deepen our understanding of cell states in aggressive tumors and their metastatic lesions in order to dissect these alternatives.

Metastasis is mainly a non-genetic process, highly dependent on instructing the host microenvironment into a nurturing niche. Stromal cells provide metastatic cells with soluble growth factors, such as Wnt or TGFβ, but also mechanical cues critical for outgrowth into lethal metastatic nodules. An example is the remodeling of ECM promoted by proteases secreted by neutrophils within DNA-scaffolded extracellular “traps” (i.e., NETosis), resulting in an increase in integrin signaling, which in turn promotes YAP/TAZ-dependent reawakening from dormancy and initiation of colonization[132] (Figure 3c). ECM stiffening of pancreatic cancer can also promote metastatic growth through YAP/TAZ-dependent metabolic reprogramming[133].

It has been noticed that metastasis in fact also represents a remarkable mechanical journey through very diverse mechanical strains, such as compression, stretching, intravasation, circulation, adhesion, extravasation and regrowth within an alien organ architecture[134]. All these mechanical stresses necessarily impact on the cells’ own mechanical state and feedback on the ability to adapt to such strains[134]. We predict that YAP/TAZ may be an integral element in such interplay. For example, loss of mechanosignaling in malignant cells

entering into the bloodstream may contribute to their metastatic inefficiency. Conversely, mechanical activation of YAP/TAZ may represent a means to avoid nuclear damage by extreme mechanical cell deformations[135,136,137]. In line with this hypothesis, evidence exists that YAP/TAZ are not only downstream of cytoskeletal inputs but also actively contribute to F-actin dynamics through expression of cytoskeletal proteins in metastatic $_{cells}$126,138,139.

YAP/TAZ and the tumor microenvironment

Activation of YAP/TAZ in tumor cells initiates iterative and bidirectional interactions with other elements of the tumor microenvironment (Figures 3d-e), that also entails YAP/TAZ activation in fibroblasts, endothelial cells and neighboring healthy epithelial cells. An emerging and particularly exciting area of investigation relates to the role of YAP/TAZ in controlling immune cell composition and activity.

Cell competition

In healthy tissues, cells that are “perceived as different” are actively eliminated through a process called “cell competition”. This phenomenon was initially described in *Drosophila* in fact in association with loss-of-function mutations in the Hippo pathway and was then recognized in mammalian systems[140,141]. Cell competition in tumors is bidirectional, with healthy tissue inhibiting cancer cell growth, and, vice-versa, with cancer cells fostering the demise of non-malignant cells to find new soil for their expansion[142]. Intriguingly, in a mouse model of cholangiocarcinoma, experimental hyperactivation of YAP/TAZ in peritumoral normal hepatocytes causes them to acquire a competitive advantage vs. tumor cells[143]. Similarly, in glioblastoma, high YAP expressing clones of normal cells acquire dominance over surrounding tumor cells[144]. These non-cell autonomous interactions might also help to reconcile recent provocative findings on APC-mutant intestinal tumor models, in which conditional depletion of YAP/TAZ mediated by Adenoviral-Cre injection in the colon mucosae has been reported to favor tumor growth[145]. Although at odds with other reports on YAP/TAZ being required for intestinal tumorigenesis[69,88,146–148], this result might be potentially explained by an overarching effect of YAP/TAZ loss in non-malignant cells loosing competitive capacity against APC-mutant clones.

Angiogenesis

Increased YAP/TAZ function also occurs in stromal cells, including cancer associated fibroblasts (CAFs), Endothelial cells (ECs) and pericytes (reviewed in Ref. 43; Figure 3d). This suggests that YAP/TAZ activation may represent a trait shared by different cells of the tumor ecosystem. In development, YAP/TAZ are fundamental drivers of vascularization[149], and this property is hijacked in cancer to support tumor survival and expansion (Figure 3d). In lung cancer allografts, high expression of YAP in the tumor endothelium induced tumor growth[150], and ECs exposed to YAP-positive tumor cells activated their own YAP/TAZ for neo-angiogenesis[151,152]. Conversely, loss of YAP/TAZ in renal cell carcinomas inhibited EC proliferation, through modulation of VEGF signaling[153]. Thus, YAP/TAZ are the centerpiece of the communication between tumor cells and tumor angiogenesis. To do so, YAP/TAZ integrate a number of inputs, such as hypoxia, through HIF1α-dependent and -independent mechanisms, and angiogenic and inflammatory cytokines. For example,

the VEGF pro-angiogenic effect has been reported to signal through the Hippo kinases to increase YAP/TAZ[154]. In turn, tumor ECs express high level of Endothelin1, that induces YAP/SMAD association and activation of inflammatory responses[155]. ECM stiffening and increased matrix metalloproteases (MMP)-mediated ECM remodeling in tumors also fuel sprouting angiogenesis[149]. Notably, increased fibrosis around tumor cells is mediated by YAP activation in CAFs, which are known to promote malignancy and angiogenesis[40] (Figure 3d). In line, treatment of CRC liver metastases with a combination of VEGF and angiotensin inhibitors reduced myofibroblast activity, lowered ECM stiffness and prevented angiogenesis, thereby limiting metastatic aggressiveness[156].

Tumor vessels derive from an aberrant and unphysiological sprouting, forming immature and disorganized networks[157], characterized by disturbed blood flow that can further contribute to YAP/TAZ activation in ECs and to endothelial inflammatory responses[158,159] (Figure 3d). In addition, tumor vessels are leaky, leading to accumulation of interstitial fluid pressure, contributing, through cell compression and stretching, to YAP/TAZ mechanical modulation[149]. Thus, targeting YAP/TAZ function in ECs and/or CAFs may be sufficient to curtail ECM-mediated, YAP/TAZ self-feeding loops, reducing fibrosis, normalizing tumor vasculature and improving effectiveness of therapies. In this aspect, it is worth considering that YAP/TAZ transcriptionally control matricellular proteins such as CTGF and Cyr61, whose targeting may be beneficial to improve chemosensitivity[160].

Crosstalk with the immune system

Immune-checkpoint inhibitors (ICI) are pillars of cancer treatment. However, a large fraction of patients does not achieve long-lasting benefits from ICI[161,162]. Intriguingly, YAP/TAZ activation in tumor cells has been shown to rewire immune responses in the TME, enabling tumor cells to escape immune surveillance (Figure 3e). As such, targeting YAP/TAZ in the TME may represent an efficient route to boost the effect of immune-directed therapies.
To start, YAP overexpression in the mouse liver fosters infiltration of protumorigenic macrophages[163,164]. Similarly, in nonalcoholic steatohepatitis, a condition that precedes hepatocellular carcinoma, TAZ activity also associates to macrophage recruitment, although functional validation of this observation is still pending[165]. In pancreatic and prostate tumors, YAP/TAZ also cause recruitment of Myeloid-derived-suppressor-cells (MDSCs), immature myeloid cells that favor anergy of effector T cells and tumor tolerance[166,167]. Vice-versa, YAP-defective tumor cells reduce MDSC recruitment. These findings are also reflected in patient data, as CRC patients with overactive YAP display increased density of MDSCs and adverse clinical features.

Similarly to CAFs and ECs, immune cell populations are also subject to the same mechanical and biochemical cues that induce YAP/TAZ activation in tumor cells, raising their own YAP/TAZ levels to promote malignancy (Figure 3e). For example, DAB2-expressing tumor-associated macrophages (TAMs) are a population of exquisitely mechanosensitive cells in which YAP/TAZ are key to “escort” tumor cells for metastatic dissemination[168]. DAB2 expression is predictive of overall patient survival in luminal B breast cancer but not in the more malignant subtypes of mammary tumors[168], potentially because less aggressive tumors are more dependent on cellular aid to invade nearby

tissues. In addition, YAP/TAZ are undetectable in naïve CD4+ T cells but upregulated in intra-tumoral Tregs where they are required to generate an immunologically cold and tolerant microenvironment[169,170]. Coherently with the above discussion, YAP genetic ablation in effector CD4+ and CD8+ T cells results in enhanced T-cell activation and tumor infiltration[171,172]. Intriguingly, YAP activation on effector T-cells is under the control of mechanotransduction, as stiffening of draining lymph nodes promotes YAP/TAZ activity and opposes the amplification of effector T-cells[173].

Targeting YAP/TAZ in cancer

In the past ten years many efforts were directed to the identification of pharmacological approaches to inhibit YAP/TAZ activity, as summarized below (Figure 4a).

Targeting YAP/TAZ expression

YAP/TAZ have been depicted as undruggable molecules; however, their expression can be experimentally decreased using RNA-interference methods. Recent chemical developments on the backbone of antisense oligonucleotides (ASOs) allowed to create reagents that are sufficiently stable to induce depletion of the desired target genes in vivo. ION537, an anti-YAP DNA ASO created by Ionis Pharmaceuticals, has been shown to effectively inhibit YAP expression and to blunt the growth of tumor xenografts[174], and it is currently undergoing a phase I trial in patients with advanced solid tumors (NCT04659096).

Targeting YAP/TAZ interaction with TEAD

The first example for this therapeutic entry point is verteporfin, a drug able to restrain YAP/TAZ binding to TEADs, dampening YAP/TAZ-induced transcription and activity[175], although its cytotoxic effects may be YAP-independent[176,177]. Several other molecules (compounds and peptides) have been identified as inhibitors of the YAP/TAZ-TEAD interaction (Figure 4b) (reviewed in Ref. 174). IAG933, an inhibitor of YAP/TAZ-mediated transcription developed by Novartis that possibly belongs to this category, is currently being evaluated in a phase I clinical trial against tumors bearing mutations on the Hippo pathway components or YAP/TAZ gene fusions (NCT04857372).

Targeting TEADs

Structural studies on TEAD proteins revealed that they contain a hydrophobic pocket, harboring a palmitoyl group covalently bound to a cysteine (Figure 4c)[178,179]. Palmitoylation is relevant for TEAD folding and stability, and thus represents a molecular entry point to blunt YAP/TAZ activity. Several YAP/TAZ-inhibitors have been indeed identified as targeting the hydrophobic pocket of TEADs (reviewed in Ref. 174). Of these, VT3989, a drug developed by Vivace Therapeutics, has entered a phase I clinical trial (NCT04665206) in solid tumors and mesotheliomas with *NF2* mutations. Intriguingly, TEAD inhibitors have been shown to be effective at causing regression of pre-established NF2 or LATS deficient mesothelioma models[180,181].

Targeting BRD4 and other BET proteins

BET-inhibitors (BETi, i.e., drugs targeting BRD4 and its family members) are promising anti-YAP/TAZ therapeutic agents, given that YAP/TAZ recruit BRD4 on chromatin. In line, BETi suppress YAP/TAZ-driven tumorigenesis in vivo[2]. A number of clinical trials have been initiated with BETi, but only few have been concluded so far (reviewed in Ref. 182), and data remain too scarce and discontinuous to draw firm conclusions.

Targeting Rho-GTPases and ROCK

Several drugs affecting the mevalonate biosynthetic pathway interfere with the geranyl-geranylation of Rho-GTPases, a modification required for their membrane anchoring. As such, these compounds may represent mechano-inhibitory drugs[30], although their effectiveness as YAP/TAZ inhibitors at pharmacological concentrations remains undetermined. Nevertheless, statins have already been noted to have beneficial effects in cancer patients, and their usage correlates with decreased cancer incidence in the general population (reviewed in Ref. 183). Of note, some clinical trials with statins also found that these drugs can enhance the effects of chemotherapy[183], warranting an in-depth clinical exploration of these “off-the-shelf” and safe compounds. Another appealing therapeutic target is ROCK1/2, that is effective at blunting YAP/TAZ in vitro and in animal models. The development of ROCK-inhibitors is a field of interest, intriguingly connected to treatment of immune disorders and fibrosis[184].

Targeting SRC family members

Compounds affecting the activity SRC and its family members (e.g., Dasatinib) are candidate mechanodrugs, and have been shown to inhibit YAP/TAZ activity in vitro and in vivo. Several of these drugs have already been tested in clinical trials on cancer patients with mixed results (reviewed in Ref. 185). Of note, pancreatic and colon cancers display the greatest propensity to respond to these treatments, although it remains unclear whether these responses could be ascribed to YAP/TAZ inhibition.

Conclusions and Perspectives

Despite remarkable insights gained in recent decades, many outstanding questions remain. First, a remarkable property of YAP/TAZ activation is to reprogram cell fates, a feature that has been studied in some detail in the regenerating intestine, in intestinal and other tissues’ organoids[17,27,31,62,69,86,88,92–95,186]. Is this exploited in other contexts, including tumors and if yes, by which means?

Second, and as evident in this Review, we still remain with quite superficial descriptions of phenotypes controlled by these transcriptional regulators, and molecular insights are limited. For example, YAP/TAZ conditional inactivation in individual cells of the tumor microenvironment, followed by longitudinal single-cell characterization of the whole tumor ecosystem may inform on YAP/TAZ-dependent changes in cell fates, dynamics and cell-cell communication. Moreover, if incorporated into spatial transcriptomic technologies, signatures of YAP/TAZ activity in individual cells may shed light on tumor 3D self-organization and maintenance, on the spatial contexture of tumor-specific cellular networks,

and on the relative positioning of tumor and stromal cells into “tissue motifs”. We believe that this may generate hypotheses on the supracellular principles that are central to tumor growth, and on the role of mechanical strains in orchestrating tumor morphogenesis.

Third, genetic analysis have focused on the role of YAP/TAZ in tumor initiation. A main unknown is whether metastases are still addicted to YAP/TAZ or whether other mechanisms may be at play to sustain an advanced tumor ecosystem. Sophisticated mouse models, combining conditional activation of oncogenes in specific cell types and subsequent conditional YAP/TAZ deletions in the same cells, are required to investigate the consequences of YAP/TAZ inactivation within highly malignant lesions.

Moreover, a particularly attractive aspect that has recently emerged is the interplay of YAP/TAZ mechanosignaling in tumor cells with myeloid and lymphoid components of the stroma. The available evidence at least suggests that targeting mechanotransduction may hit, at once, a vulnerability shared by all these cells, and turn immunologically cold tumors into hot. If true, this scenario would incentivize testing combinations of YAP/TAZ inhibitors and ICI in the clinical setting.

The emergence of novel, first in class therapeutics targeting YAP/TAZ is, given all the above, an exciting news for the field. However, there are two notes of caution. First, our knowledge on YAP/TAZ biology is largely centered on epithelial cells and epithelial-specific conditional mutants in mouse models; these studies revealed the inconsequentiality of YAP/TAZ for normal cells, and their paramount relevance for tumor cells. It is from these results that the idea of targeting YAP/TAZ was proposed as a candidate “silver bullet” for cancer therapy. However, this is an oversimplification and potentially an overstatement: we recently reported that endogenous YAP/TAZ mechanotransduction does play physiological roles in fibroblasts and smooth muscle cells, preventing aging-related degeneration in a variety of organs[137]. This may result in toxicities associated with long-term treatment with YAP/TAZ inhibitors. The second potential concern relates to the emerging role of YAP/TAZ as supporters of Tregs and inhibitors of effector T-cells. Systemic inactivation of YAP/TAZ may outbalance immune tolerance in multiple organs, favoring the rise of auto-immunity and inflammatory diseases. Tempering these concerns may require a regimen of YAP/TAZ inhibition either very short or delivered to targeted cell types.

Finally, although we have so far dealt with “YAP/TAZ” as if they were a unique entity, as justified by the vast redundancy between two factors, we also believe that time is finally ripe to discriminate the specificities of YAP vs. TAZ in the multifaceted tumor biology, and pioneering efforts in this direction are starting to emerge[80,81,187]. Targeting just one of these two factors, for example by using gene-specific RNA-therapeutics, could allow to limit unwanted effects on healthy tissues while retaining effectiveness against cancer.

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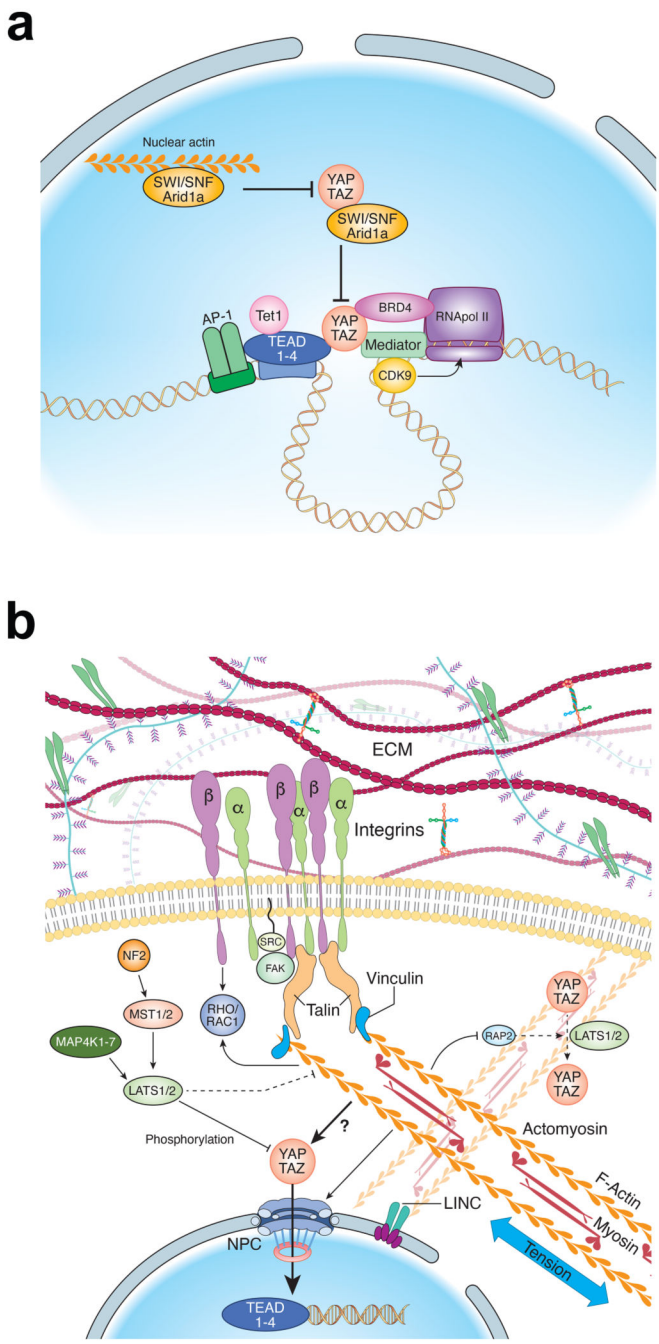

Figure 1. YAP/TAZ regulation inside and outside the nucleus.

a) Regulation of YAP/TAZ transcriptional activities inside the nucleus. YAP/TAZ are transcriptional co-factors that are recruited to enhancer elements on chromatin by TEAD proteins, and act in concert with other transcription factors (e.g. AP-1) to assemble chromatin modifiers and readers, ultimately promoting Pol II elongation on the promoter elements of cognate genes. In absence of mechanical stimulation, the SWI/SNF complex interacts with YAP/TAZ, impeding their binding to TEADs. Mechanical tension on the cells

induces the formation of nuclear actin filaments that sequester SWI/SNF complexes away from YAP/TAZ, thus contributing to YAP/TAZ activation.

b) YAP/TAZ regulation by mechanotransduction and Hippo signaling. Cells respond to ECM rigidity by adjusting their tensional state through integrin-mediated cell–ECM Focal adhesions (FAs). FAs connect the ECM with the intracellular F-actin cytoskeleton in a manner involving the FAK and Src kinases and cells increases actomyosin tension and restructures its entire cytoskeleton in a process requiring Rho-GTPases (such as Rho or Rac1), myosin motors and ROCK. The actomyosin tension transduces physical inputs into modulation of YAP/TAZ nuclear–cytoplasmic shuttling. The F-actin cytoskeleton impacts also on the mechanics and shape of the nucleus through LINC complexes, favoring YAP/TAZ nuclear entry by inducing nuclear deformation. RhoGEFs, Rho guanidine nucleotide exchange factors; ROCK, Rho-associated protein kinase; FAK, Focal adhesion Kinase; LINC, Linker of nucleoskeleton and cytoskeleton.

The Hippo pathway inhibits YAP/TAZ either through direct phosphorylation of these proteins by LATS1/2, or indirectly, by influencing the actin cytoskeleton. In turn, acto-myosin contractility can affect LATS1/2 activity trough the GTPase RAP2.

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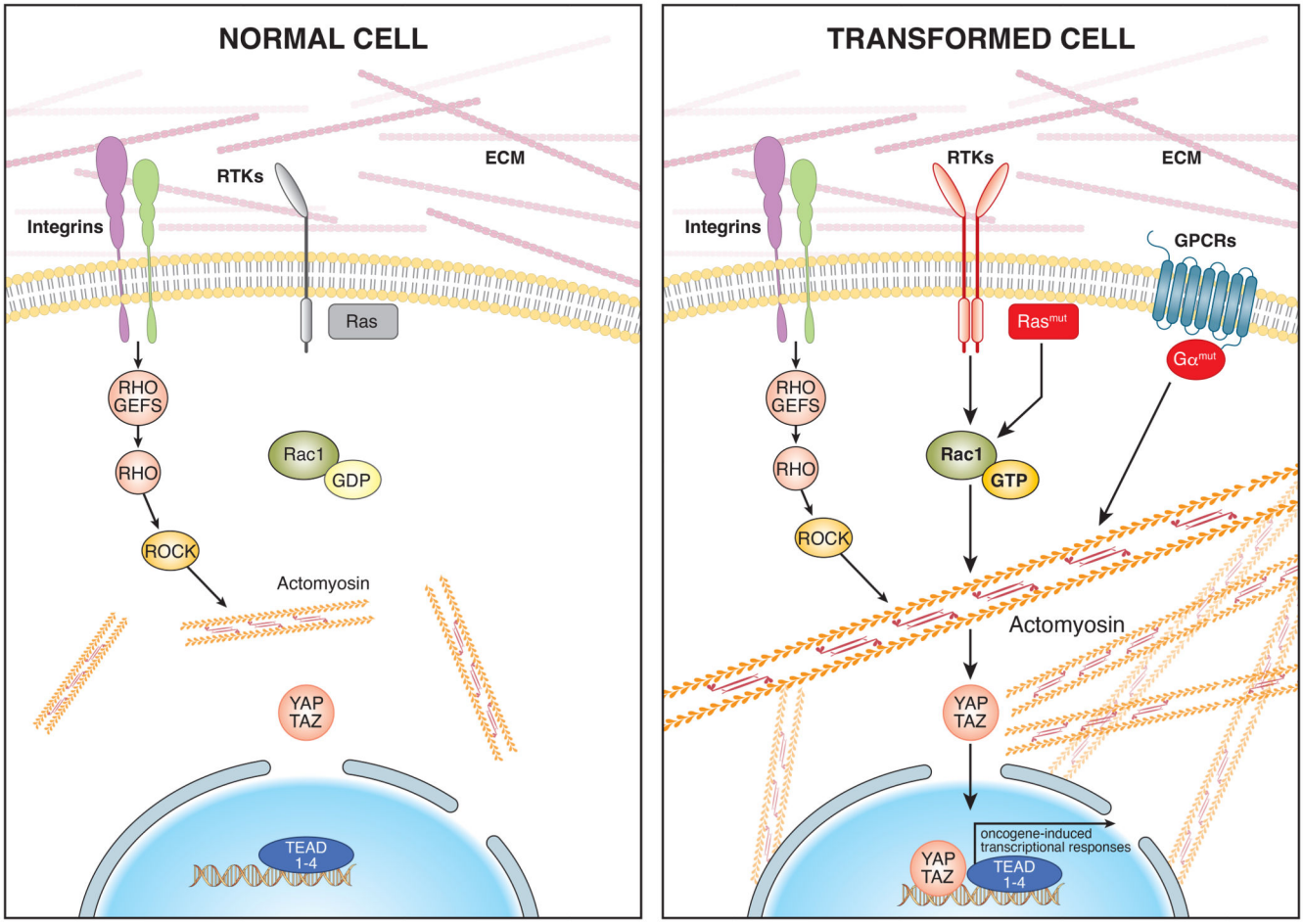

Figure 2. Synergistic effects of oncogenes and mechano-signaling on YAP/TAZ activation in cancer.

Oncogenic mutations promote the assembly of robust acto-myosin contractile structures in cooperation with mechanical stimulations from the microenvironment, eventually leading to YAP/TAZ activation and cell transformation. In the absence of either oncogenes or substantial mechanical stimulation, cells do not accumulate contractile microfilaments and nuclear YAP/TAZ; thus transformation does not occur.

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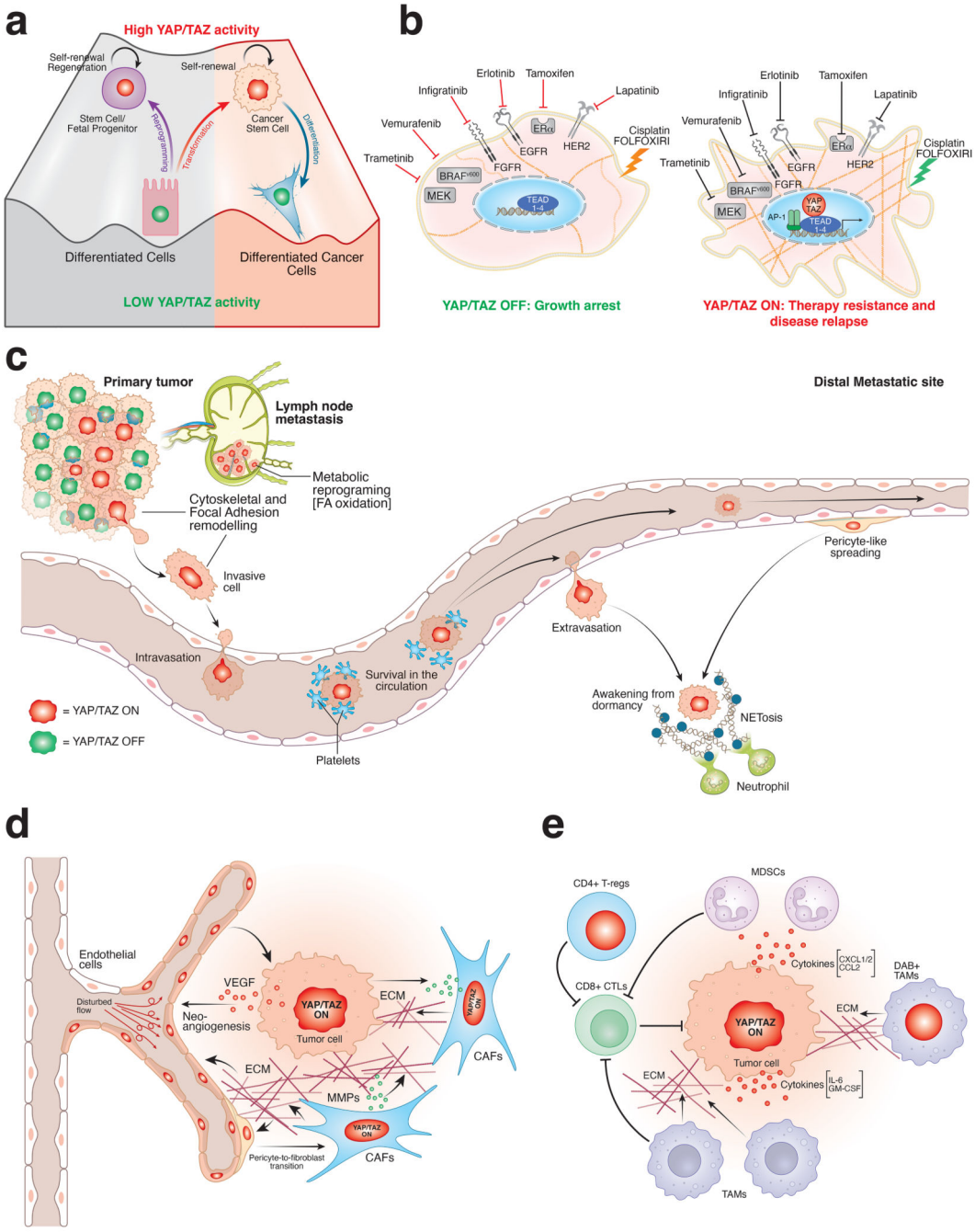

Figure 3. The hallmarks of YAP/TAZ activity in cancer.

a) YAP/TAZ activity (red nuclei) can promote differentiate cells to acquire a stem-like or a cancer stem cell identity, as depicted by cell-fate transition in the Waddington epigenetic landscape. Conversely, loss of YAP/TAZ activity in cancer stem cells would cause differentiation toward a less aggressive phenotype.

b) High mechanical stimulation promotes resistance against a number of targeted therapies and chemotherapeutic regimens through activation of YAP/TAZ. Conversely, YAP/TAZ inhibition sensitizes cancer cells to these same treatments.

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c) Schematic representation of the metastatic cascade, showing the involvement of YAP/TAZ in the various steps of the metastatic journey, including cell migration from the primary tumor, growth of local metastases in the lymph nodes, intravasation, survival in the circulation trough mechanical crosstalk with platelets, extravasation, spreading in the metastatic site, and awakening from dormancy.

d) YAP/TAZ activation (red nuclei) in tumor stromal components leads to neo-angiogenesis and conversion of fibroblasts and pericytes into Cancer-Associated Fibroblasts (CAFs). In turn, the restructuring of the tumor microenvironment by CAFs induces mechano-activation of YAP/TAZ in tumor cells, which secrete factors further promoting these feed-forward interactions.

e) YAP/TAZ-mediated crosstalk between tumor cells and the immune cells in the tumor ecosystem. YAP/TAZ activity in cancer cells promotes immunosuppression through the recruitment of Myeloid-Derived Suppressor Cells (MDSCs) and Tumor-Associated Macrophages (TAMs). Immunosuppression is further promoted by YAP/TAZ activation in Tregs. YAP/TAZ activity in TAMs also promotes tumor growth by fostering ECM deposition.

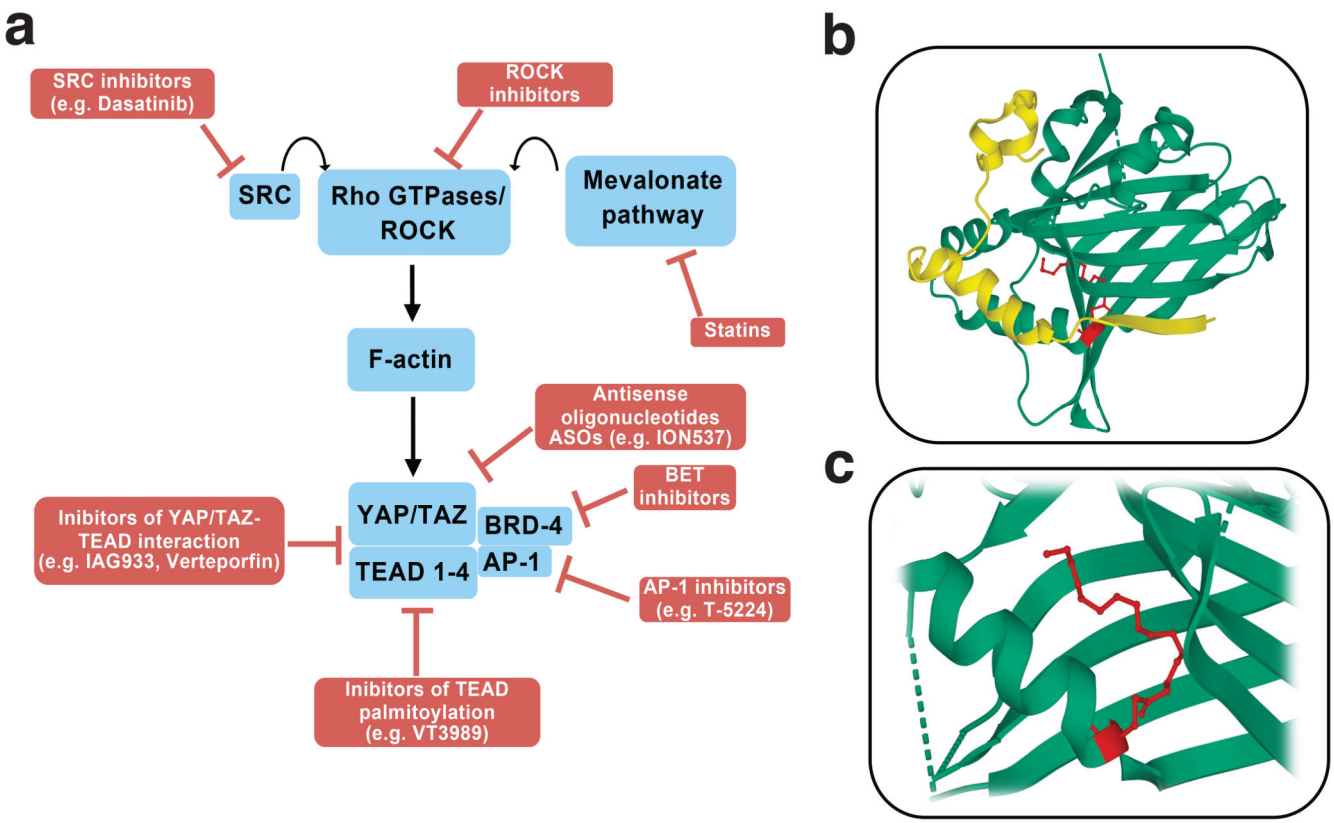

Figure 4. Targeting YAP/TAZ in cancer.

a) Schematics of the most promising molecular drugs targeting YAP/TAZ activity. Red boxes highlight inhibitors of specific elements of YAP/TAZ mechanotransduction (in light blue boxes).

b) Ribbon diagram showing the conserved carboxy-terminal YAP-binding domain of TEAD protein. YAP is shown in yellow and TEAD in green. Image from the RCSB PDB (rcsb.org) of PDB ID 3KYS[188], created using Mol* Viewer[189].

c) Ribbon diagram showing the hydrophobic pocket of TEAD protein hosting a palmitoyl group covalently bound to a cysteine. Palmitoylated cysteine is shown in red and TEAD in green. Image from the RCSB PDB (rcsb.org) of PDB ID 5emv[190], created using Mol* Viewer[189].

Table 1
Consequences of YAP/TAZ activation across cancer types

Patient data	Murine cancer models	Human cancer models
Breast Cancer (BC)		
Gene signatures for YAP/TAZ activity correlate with poor differentiation, enrichment of cancer stem cell signatures, metastasis proclivity, and poor patient outcome (reviewed in [42]). TAZ protein expression and nuclear localization is associated to poor differentiation and it is prognostic of poor clinical outcome (reviewed in [42]).	Genetic loss of Yap greatly increases the latency while reducing the growth and metastatic proclivity of mammary tumors arising in MMTV-PyMT mice[6]. YAP/TAZ deletion abolishes tumor initiation triggered by APC knockout in the mammary gland[2]. YAP overexpression confers metastatic abilities to otherwise benign mouse mammary cancer cells[122].	TAZ knockdown suppresses tumor formation by MCF7 cells (reviewed in [42]). TAZ overactivation confers CSC and malignant properties to otherwise benign MCF10AT cells, whereas TAZ knockdown reduces tumor growth of the malignant MCF10ACA1 cell line[57]. TAZ is required for metastasis formation by primary human BC cells injected in the orthotopic site[107]; YAP is required for metastasis formation by intracardiacal-injected HCC1954 or MDA-MB-231 cells[131].
Non-Small Cell Lung Cancer (NSCLC)		
Gene signatures for YAP/TAZ activity correlate with poor patient outcome (reviewed in [42]). Cells with elevated YAP and TAZ protein expression are enriched in lung adenocarcinomas (LUADs, 76% of cases) and lung squamous cell carcinomas (LUSCCs, 65%of cases), respectively, and are associated with shorter patient survival (reviewed in [42]).	In mice, YAP overexpression in $Kras^{G12D}$-induced lung adenomas promotes their progression to LUAD; conversely, YAP knockout inhibits tumor progression from adenoma to LUAD and LUSCC in the $Kras^{G12D}/Lkb1^{KO}$ mouse model[59].	TAZ depletion represses lung tumor formation by tail vein-injected A549 LUAD cells (reviewed in [42]). YAP depletion suppresses brain metastasis formation by intracardiacal-injected H2030 LUAD cells[131].
Colo-Rectal Cancer (CRC)		
Gene signatures for YAP/TAZ activity correlate with poor patient outcome (reviewed in [191] and in [42]). YAP/TAZ mRNA and protein expression are upregulated in CRCs compared to the normal tissue, and elevated YAP/TAZ expression is prognostic of shorter patient survival (reviewed in [42]).	YAP or TAZ knockout severely compromises tumor initiation in the intestine of APC^{min} mice[63,69].	YAP is required for the growth of tumors formed by HCT116 cells in the orthotopic site and by SW620 cells in xenografts[146,147].
Gastric cancer (GC)		
YAP/TAZ protein expression is upregulated in GCs compared to the normal tissue, and elevated YAP/TAZ expression is prognostic of shorter patient survival (reviewed in [42]).	A peptide inhibitor of YAP/TAZ-TEAD interaction strongly decreases gastric adenoma formation induced by the mutagen MNNG combined with *Helicobacter pylori* infection (reviewed in [42]).	YAP depletion inhibits tumor growth and metastatic dissemination of SGC7901 cells injected in the orthotopic site[192].
Hepatocellular Carcinoma (HCC)		
High levels of nuclear YAP are found in about 66% of cases, and this is associated with poor differentiation and short patient survival (reviewed in [42]).	In vivo depletion of YAP via siRNAs causes regression of advanced HCC lesions induced by sporadic MST1/2 knockout in hepatocytes (reviewed in [42]).	YAP depletion reduces tumor growth in a PDX model of HCC [193].
Pancreatic Adenocarcinoma (PDAC)		
Nuclear YAP is detected in 90% of cases and its overexpression correlates with shorter patient survival[194].	YAP/TAZ are required for pancreatic tumor initiation and progression to PDAC in the $KRas^{G12D}/p53^{KO}$ mouse model[27,104]	YAP depletion suppresses tumor initiation by xenografts of BxPC-3 cells[194].
Prostate Cancer (PC)		
YAP and TAZ are nuclear in the majority of PCs (>60%), and the frequency of cells with nuclear YAP/TAZ increases with grade; elevated YAP expression is predictive of poor patient outcome[195,196]	YAP overexpression in the prostate epithelium is sufficient to induce age-related PC induction (reviewed in [42]).	YAP depletion impairs the growth of xenografted C4-2 cells (reviewed in [42]). TAZ depletion impairs the growth of xenografted PC-3 cells[195].

Patient data	Murine cancer models	Human cancer models
Cutaneous Squamous Cell Carcinoma (CSCC)		
YAP/TAZ are nuclear in the majority of cases[197,198]	YAP/TAZ knockout impedes CSCC formation induced either by chemical carcinogenesis or by forced expression of oncogenic KRAS in the epidermis[91,197].	YAP depletion suppresses the growth of tumors formed by xenografted A431 cells[198].
Basal Cell Carcinoma (BCC)		
YAP and TAZ are found in the nucleus of BCC cells in >90% of patients[197,198]	YAP/TAZ are required for the development of BCCs triggered by overactivation of the shh pathway in epidermal basal cells[197,199].	
Melanoma (MEL)		
Cutaneous (CMEL): YAP is found in the nuclei of benign nevi and CMELs (reviewed in [42]). In lymph node (LN)-positive CMELs, elevated nuclear YAP in the cells of the invasive front correlates with distant metastasis proclivity[125]. The pro-metastatic invasive cell state of CMEL is driven by YAP/TAZ/TEAD (reviewed in [42]). Uveal (UMEL): nuclear YAP is found in the majority of cells of Gαq/11-mutant tumors, enlisting about 66% of UMELs[26,46]	YAP depletion impairs lymph node metastasis of the mouse CMEL cell line B16F10[125]	YAP or TAZ depletion inhibits metastatic colonization of the lung by tail-vein injected 1205Lu CMEL cells(reviewed in [42]), and the growth of some PDX models of CMEL[200] YAP depletion impairs the growth of tumors formed by xenografted Gαq/11-mutant UMEL cells[26,46]
Glioblastoma Multiforme (GBM)		
TAZ expression is prognostic of shorter patient survival (reviewed in [42]). Nuclear TAZ is invariably found in the cells surrounding the necrotic core of GBMs; expression of a YAP/TAZ-driven GBM stem cell signature is prognostic of shorter patient survival[101]	YAP/TAZ depletion abolishes GBM initiation in the orthotopic site by oncogene-transformed glioma cells, and by GL261 and CT2A mouse GBM cell lines[101]	YAP/TAZ depletion abolishes tumor initiation in the orthotopic site by primary GBM cell lines [101] (see also [42]).
Osteosarcoma (OS)		
Nuclear YAP is found in 46% of OSs and is prognostic of worse patient outcome[201].	YAP depletion inhibits subcutaneous growth of primary mouse OS cells (reviewed in [42])	YAP depletion inhibits subcutaneous growth of MG-63 and of HOS cells (reviewed in [42]).
Soft-Tissue Sarcoma (STS)		
Nuclear YAP or TAZ staining is found in 55% and 33% of STSs, respectively[202].	YAP depletion reduces subcutaneous growth of tumors formed by primary mouse STS cells (reviewed in [42]).	
Rhabdomyosarcoma (RMS)		
Nuclear YAP is detected in 36% of Alveolar RMS (ARMS) and in 73% of Embryonal RMS (ERMS) (reviewed in [42])	YAP overexpression in satellite cells induces the formation of ERMS (reviewed in [42]).	YAP depletion reduces tumor growth by xenografted RD ERMS cells (reviewed in[42]).

Table 2

Human tumors displaying genetic alterations in Hippo pathway components or in YAP/TAZ

Affected gene	Consequence on YAP/TAZ enrichment	Functional Evidence
Human tumors displaying genetic alterations in Hippo pathway components		
Malignant Mesothelioma (MM)		
NF2 (19% inactivating mutations; 19% CNL; 7% inactivating fusions) *STK4* (*MST1*; 16% CNL) *SAV1* (12% CNL) *LATS1* (20% CNL) *LATS2* (1% inactivating mutations; 5% CNL) (reviewed in [4]).	YAP staining is negative in normal pleural samples, but positive in 93% of MM samples[203].	Mice develop MMs after combined ablation of *Nf2* and *Cdkn2a* or *Nf2* and *Tp53* in mesothelial cells[204]. The development of asbestos-induced MMs is greatly accelerated in mice lacking one allele of *Nf2*[205]. YAP depletion inhibits the invasive and clonogenic abilities of H290 and H2052 *NF2*-mutant human MM cells[203].
Sporadic Meningioma		
NF2 (~45% inactivating mutations combined with LOH) (reviewed in [4])	YAP is highly expressed and localizes in the nucleus of tumor cells in 100% of human meningiomas of all grades[106].	Patients with germline heterozygous mutation of *NF2* develop neurofibromatosis type 2, which includes the development of meningiomas associated to LOH of *NF2*[206]. In mice, biallelic loss of *Nf2* in cells of the arachnoid leads to development of meningiomas[207]. YAP knockdown suppresses in vitro proliferation and migration of human meningioma cells[106].
Sporadic Schwannoma		
NF2 (77% inactivating mutations and/or CNL) ((reviewed in [4]).	YAP is found in the nucleus of schwannoma cells in 100% of cases (reviewed in [42]).	Patients with germline heterozygous mutation of *NF2* develop neurofibromatosis type 2, which includes the development of schwannomas associated to LOH of *NF2*. [206] Mice with biallelic loss of *Nf2* in Schwann cells develop manifestations of neurofibromatosis type 2, including development of schwannomas[208].
Sporadic Spine-Ependymoma (SP-EPN)		
NF2 (39% inactivating mutations) (reviewed in [4]).		Patients with germline heterozygous mutation of *NF2* develop neurofibromatosis type 2, which includes the development of ependymomas associated to LOH of *NF2*.[206] In mice, loss of Lats1/2 in Neural Stem Cells (NSCs) induces formation of EPNs in a YAP/TAZ-dependent manner[209].
Renal-Cell Carcinoma (RCC)		
Papillary (pRCC): *NF2* (6% inactivating mutations) *SAV1* (3% inactivating mutations) (reviewed in [4]) Sarcomatoid clear cell (sccRCC): *NF2* (12% inactivating mutations) *LATS2* (6% inactivating mutations)[210] Mucinous tubular and spindle cell (mtscRCC): *NF2* (23% biallelic inactivating mutations) *SAV1* (4.5% biallelic inactivating mutations) *PTPN14* (32% biallelic inactivating mutations)[211].	YAP is found nuclear in 90% of mtscRCC cases[211].	In mice, biallelic loss of *Nf2* or deletion of both *Lats1* and *Lats2* in adult kidney epithelia induces formation of malignant RCCs[212,213]. NF2 reconstitution or YAP knockdown in *NF2*-deficient sccRCC cells restrains proliferation and invasion in vitro and tumor growth in vivo[210].
Intrahepatic Cholangiocarcinoma (ICC)		
SAV1 (~10% CNL) *NF2* (9% inactivating mutations) (reviewed in [4])	YAP is found nuclear in 71% of ICC cases, and this is predictive of poor patient survival[214].	In mice, homozygous knockout of *Sav1* or *Nf2* in liver cells causes biliary cell reaction, later developing in liver tumors, including ICCs. These events are rescued by concomitant deletion of *Yap1*. (reviewed in [42]).
Human tumors displaying genetic alterations in YAP and/or TAZ (WWTR1)		

Affected gene	Consequence on YAP/TAZ enrichment	Functional Evidence
Cervical Carcinoma		
YAP1 (12-16% focal amplifications) *WWTR1* (8% focal amplifications)[75]	YAP is weakly expressed by normal cervical tissue, but it is overexpressed by 91% of cervical carcinomas[215].	Expression of transgenic YAP-S127A in the basal cells of the cervix induces development of invasive cervical carcinomas in mice[215].
Head and Neck Squamous Cell Carcinoma (HNSCC)		
YAP1 (6% focal amplifications) *WWTR1* (9% focal amplifications) [75]	TAZ is overexpressed and nuclear in 50% of oral HNSCC samples, and is predictive of poor patient survival (reviewed in [42]).	YAP and TAZ are required for tumor formation by HNSCC cells transplanted in the orthotopic site (tongue) (reviewed in [42]). YAP and TAZ are required for the fitness of distinct types of oral HNSCC cell lines, with TAZ being required in cells displaying amplification of *WWTR1*[216]
Esophageal Squamous Cell Carcinoma (ESCC)		
YAP1 (6% focal amplifications) *WWTR1* (27% focal amplifications) [75]	60-90% of ESCC samples display nuclear YAP and TAZ staining. Nuclear expression of YAP is predictive of poor survival in ESCC patients (reviewed in [42]).	YAP is required for proliferation of ESCC in vitro (reviewed in [42]).
Ovarian Serous Cystadenocarcinoma (OV)		
YAP1 (8% focal amplifications) [75]	49% of OV display elevated expression of YAP, mostly in the nucleus[217]	Overexpression of YAP converts cells of the fallopian tube (the cells-of-origin of ovarian cancer) into high-grade serous carcer cells able to form tumors in vivo (reviewed in [42]).
Hemangio-Endothelioma (HE)		
Epithelioid (EHE): *WWTR1* (~90% gene fusion with *CAMTA1*). *YAP1* (8% gene fusion with *TFE3*) (reviewed in [79]). Retinoid (RHE): *YAP1* (38% fusion with *MAML2*) (reviewed in [79]). Composite (CHE): *YAP1* (27% fusion with *MAML2*) (reviewed in [79]).	TAZ-CAMTA1 is found in the nucleus in ~90% of EHEs. 7% of EHEs display nuclear YAP-TFE3 (reviewed in [79]).	Transgenic *WWTR1-CAMTA1* expression in endothelial cells induces development of HE in mice[77,78].
Supratentorial Ependymoma (ST-EPN)		
YAP1 (5% gene fusions, 86% of which with *MAMLD1*, and 14% with *FAM118B*) (reviewed in [79]).		Transgenic expression of the YAP-MAMLD1 or YAP-FAM118B in NSCs induces formation of ST-EPN in mice (reviewed in [79]).
Poroma/Porocarcinoma		
Poroma: *YAP1* (20.2% fusion with *NUTM1*, 68.3% fusion with *MAML2*) *WWTR1* (1% fusion with *NUTM1*) Porocarcinoma: *YAP1* (54.6% fusion with *NUTM1*, 9.1% fusion with *MAML2*) (reviewed in [79]).	Nuclear YAP/TAZ is detected in 96% of poromas and 64% of porocarcinomas (reviewed in [79]).	YAP1-MAML2, YAP1-NUTM1, and WWTR1-NUTM1 can promote fibroblast transformation in soft agar assay (reviewed in [79]).
Hybrid Low-grade Fibromyxoid Sarcoma/Sclerosing Epithelioid Fibrosarcoma		
YAP1 (75% fusion with *KMT2A*) (reviewed in [79]).		