

Review Article

The Hippo pathway in cancer: YAP/TAZ and TEAD as therapeutic targets in cancer

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Tumorigenesis is a highly complex process, involving many interrelated and cross-acting signalling pathways. One such pathway that has garnered much attention in the field of cancer research over the last decade is the Hippo signalling pathway. Consisting of two antagonistic modules, the pathway plays an integral role in both tumour suppressive and oncogenic processes, generally via regulation of a diverse set of genes involved in a range of biological functions. This review discusses the history of the pathway within the context of cancer and explores some of the most recent discoveries as to how this critical transducer of cellular signalling can influence cancer progression. A special focus is on the various recent efforts to therapeutically target the key effectors of the pathway in both preclinical and clinical settings.

Introduction

The Hippo pathway is an evolutionarily conserved signalling cascade regulated by a broad spectrum of upstream effectors and acts as an integral mechanosensory component of cells, transducing physical signals at the plasma membrane and regulating response via control of differentiation and proliferation in cells [1–3]. The pathway was initially discovered in *Drosophila melanogaster* following identification of core genes regulating organ size control and cellular overgrowth via mosaic screening. Genes identified include Warts (*Wts*, *LATS1/2* in human) [4,5] and Hippo (*Hpo*, or *STK4/3* encoding *MST1/2* in human) [6,7], which encode the kinases that constitute the phosphorylation cascade central to the Hippo pathway, which is a central regulator of early stage development in embryogenesis. This role is evidenced by the early embryonic lethality observed when the primary, downstream transcriptional activators of the pathway, Yap (encoded by *Yap1*) and Taz (encoded by *Wwtr1*), are both lost in mice [8]. In such cases, embryos fail to progress past morula stage, likely due to the role both gene products play in lineage specification during embryogenesis. Moreover, just homozygous loss of *Yap* results in extreme morphological disruption in mouse embryos and an inability to survive beyond embryonic day 10.5 [9]. The Hippo gene (*Hpo*) was named due to the highly proliferative overgrowth phenotype upon loss-of-function mutation of the *Hpo* gene and consequently observed increased head size in the *Drosophila*; this phenotype somewhat resembled a Hippo head under the microscope [6,7,10]. A similar, general effect is observed on loss-of-function mutations of the other core kinase cascade members. These kinases and scaffolding components act as the primary regulators of the Hippo signalling pathway, whose activities are involved in a variety of oncogenic processes and pathways [11,12]. Its close involvement with regenerative and pro-cancerous functions have made the Hippo signalling pathway an attractive, although challenging, target for drug discovery efforts of late [13].

The Hippo pathway itself consists of two primary modules: the core serine/threonine kinase cascade, which is modulated by a variety of upstream signals, and the transcriptional module that drives the expression of downstream target genes (Figure 1). Throughout the course of vertebrate evolution, duplication events have resulted in multiple paralogues of various Hippo family components [14,15]. The classical

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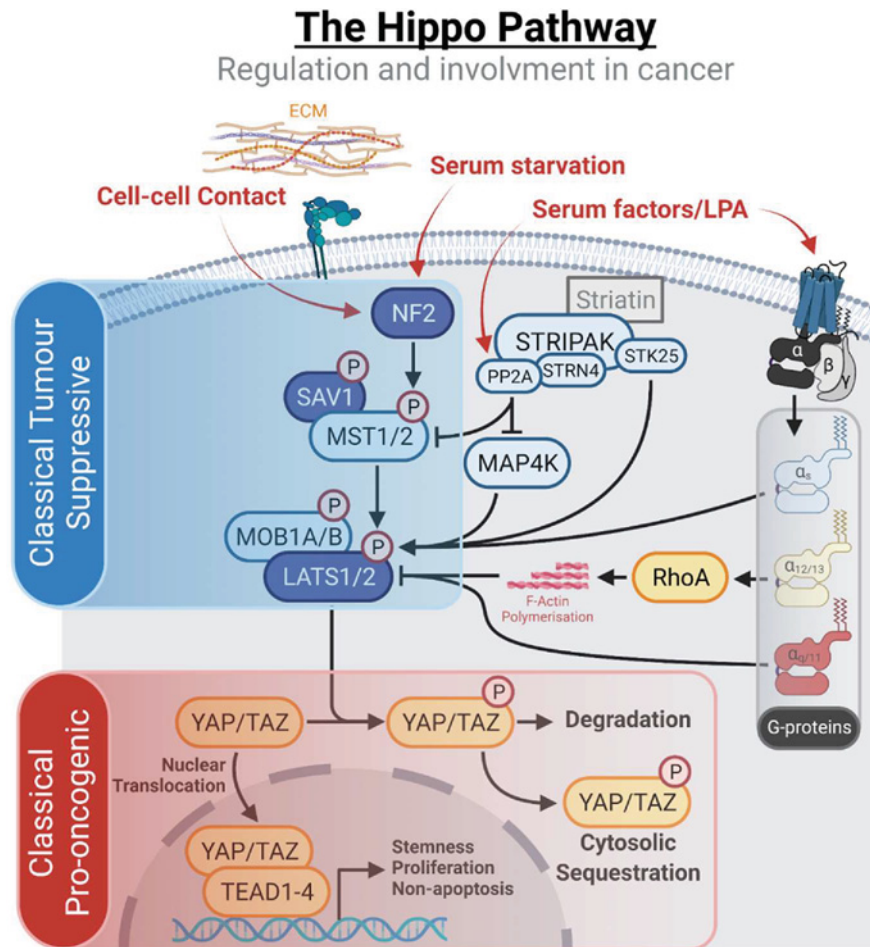


Figure 1. The Hippo pathway consists of distinct oncogenic and tumour suppressive modules

Schematic of the core Hippo pathway, including the generally tumour suppressive core kinase module (highlighted in blue) and tumorigenic transcriptional module (highlighted in red). A selection of upstream, regulatory components are additionally included. Protein products of genes frequently mutated in various specific tumour types are shown in darker colours. Note that MST1/2 are encoded by *STK4/3* respectively and TAZ by *WWTR1*.

core kinase cascade consists of MST1/2 (Hippo or Hpo) and its binding partner SAV1 (Salvador), which act to phosphorylate and activate LATS1/2 (Warts or Wts) and its binding partners MOB1A/B (Mob) [16]. Multiple additional upstream components of the kinase cascade have been described, with examples including KIBRA and NF2 (Merlin) that form spatially regulatory and kinase activating scaffolds that consequently increase LATS/MST activity [17–19]. More recently, the mitogen-activated kinase kinase kinase kinase (MAP4K) family of kinases, which act as upstream activators of the generally tumorigenic MAPK pathway [20], have also been shown to play an integral role in activating the Hippo kinase cascade, directly phosphorylating and activating LATS1/2, in parallel with the Hippo kinases MST1/2 [21]. This interaction is regulated by STRN4 (or zinedin) [22,23], a member of the striatin-interacting phosphatase and kinase (STRIPAK) complexes, which act as general regulators of a range of pathways active in cancer development [24]. The STRIPAK complex is a heterogeneous and adaptable core complex with a central regulatory role within the Hippo pathway [3], acting to modulate the activity of Hippo pathway kinases at multiple levels [25] beyond just through MAP4K-mediated cascade activation. One major arm of this involves the catalytic subunit of the protein phosphatase 2 (PP2A) family of serine/threonine phosphatases, which mediates a wide variety of cellular dephosphorylation events [26]. The PP2A catalytic subunit directly associates with MST1/2, as well as MAP4K, dephosphorylating and inactivating core kinase cascade members [23,27]. Additionally, serine threonine kinase 25 (STK25), a STRIPAK-associated GCKIII kinase, can act to both inhibit and activate the Hippo kinase cascade respectively via direct phosphorylation of SAV1, thereby inhibiting SAV1’s inhibitory role within the STRIPAK’s complex [28], as well as via directly phosphorylating and activating LATS1/2 [29].

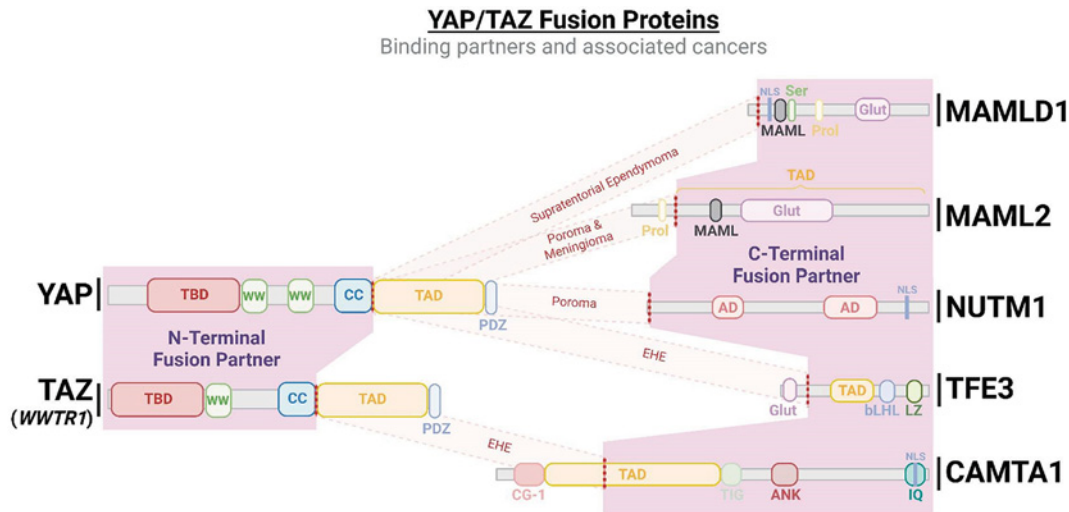


Figure 2. YAP/TAZ fusion partners and associated cancers

Protein schematics showing the structures and domains of YAP/TAZ proteins (left) and common fusion partners in specific cancers (right). The location of frequent fusion breaks are denoted (red dashed lines), with common fusions and associated cancer types highlighted in red resulting in chimeric transcription factors. TAZ is encoded by *WWTR1*. Abbreviations: AD, acidic domain; ANK, ankyrin repeat region; bLH, basic helix–loop–helix; CC, coiled-coil domain; CG-1, CG-1 DNA-binding domain; Glut, glutamine-rich region; IQ, IQ calmodulin-binding motif; LZ, leucine zipper; MAML, mastermind-like domain; PDZ, PDZ-binding domain; Prol, proline-rich region; ser, serine-rich region; TIG, transcription factor immunoglobulin domain.

From a functional perspective, the kinase module generally acts in a tumour suppressive manner, phosphorylating and inactivating the transcriptional module members, YAP (Yorkie or Yki) and its paralogue TAZ (encoded for by *YAP1* and *WWTR1* genes respectively), which were identified as oncogenes shortly after their initial discovery [30,31]. Phosphorylated and inactive YAP/TAZ are retained in the cytoplasm of the cell and subsequently degraded. In the absence of an active kinase cascade, nuclear YAP/TAZ binds to the TEAD family of transcription factors, consisting of TEAD1–4 (Scalloped or Sd), which serve to activate the expression of pro-proliferative and survival enhancing gene programs [32–35]. Post-translational modifications are critical in the regulation of the Hippo pathway, with the core kinase cascade acting through sequential serine/threonine phosphorylation of its members to ultimately phosphorylate and inhibit YAP/TAZ on multiple residues. These include five core serine residues in YAP that when collectively mutated to phosphorylation-resistant alanine, result in a hyperactive YAP protein [36]. Phosphorylation at serine residue 127 has generally been most commonly studied in relation to YAP activity as relates to oncogenesis, partly due to the ability of this phosphorylation step to inhibit *in vitro* transformation [37], while it has also been found necessary for 14-3-3 protein binding [36], with 14-3-3 a known mediator of cytoplasmic retention [38]. Pragmatically, serine YAP 127 is likely also the most studied phosphorylation site due to well-functioning, commercially available site-specific antibodies. YAP is further regulated by a variety of tyrosine kinases, including Src-family kinases c-Src and YES1, which phosphorylate YAP at multiple positions, though predominantly Y357, driving YAP activation and transcription of anti-apoptotic [39] and regenerative [40] genes, as well as transformation [41], while inhibiting transcription of genes involved in differentiation [42]. Conversely, there is evidence to suggest that c-Abl-mediated phosphorylation of YAP at Y357 induces pro-apoptotic genes in response to DNA damage [43], suggesting a context-specific role of tyrosine phosphorylation in YAP activity related to tumorigenesis. Beyond regulation via phosphorylation, TEAD activity has recently been found to be dependent on nuclear/cytoplasmic translocation [44] as well as palmitoylation [45,46], a post-translational modification by which proteins are tagged by a fatty acid side chain. It has been suggested that TEAD has the capacity to palmitoylate itself [47], with this autopalmitoylation facilitating activity, as it functions to increase protein stability. The variety of kinase activators and activating markers observed across the pathway highlights the diversity in the signals regulating activity of the core Hippo pathway components.

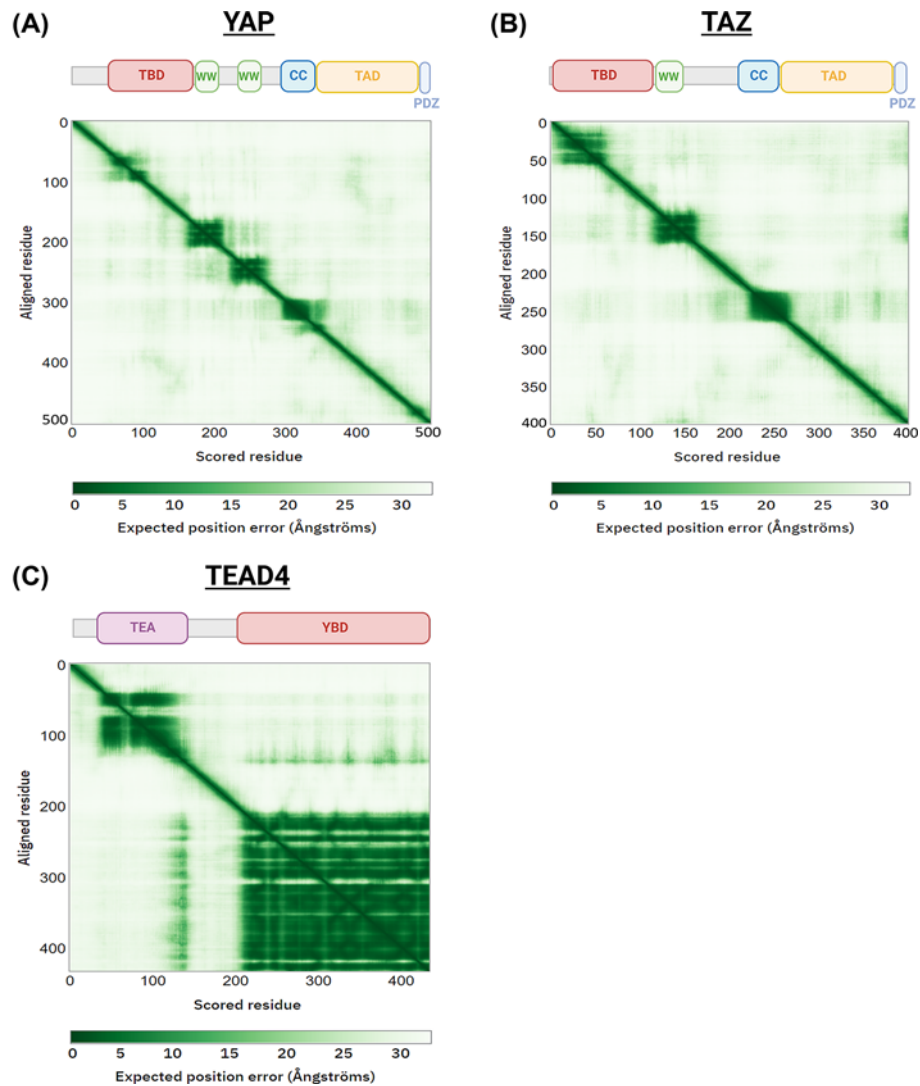


Figure 3. Intrinsic disorder of YAP and TAZ

(A) Schematic of YAP protein structure, overlaid on to AlphaFold prediction expected position error of folded domains. Darker colours show a higher confidence in predicted relationship between residues. In general, a high level of predicted error persists throughout the various YAP domains, with just WW and CC domains exhibiting high levels of structural predictability. (B) Schematic of TAZ, as in (A), highlighting the high levels of intrinsic disorder that exists outside WW and CC domains. (C) Schematic of TEAD4, as in (A), with a higher degree of confidence in protein structure prediction observed throughout, as compared with YAP and TAZ proteins, suggesting a higher degree of structural order in TEAD4. Abbreviations: CC, coiled-coil domain; PDZ, PDZ-binding domain; TEA, TEA domain; YBD, YAP-binding domain.

Hippo pathway dysregulation in cancer Genomic perturbation of kinase cascade

Although the Hippo signalling pathway is commonly dysregulated across a range of cancer types, mutations within the pathway are relatively rare: elements of the core kinase module are inactivated via mutation in common cancer types, though these are relatively infrequent events, typically present in <10% cancer cases [12,48]. However, the pathway's direct ability to drive cancer onset and development are highlighted in both animal models, where YAP/TAZ hyperactivity drives onset of multiple types of cancer and metastasis, and in some rare varieties of human cancers, where loss-of-function mutations and deletions of kinase module genes are common (Table 1). In general, mutations within the Hippo pathway are somatic, potentially due to the importance of the pathway in regulating early

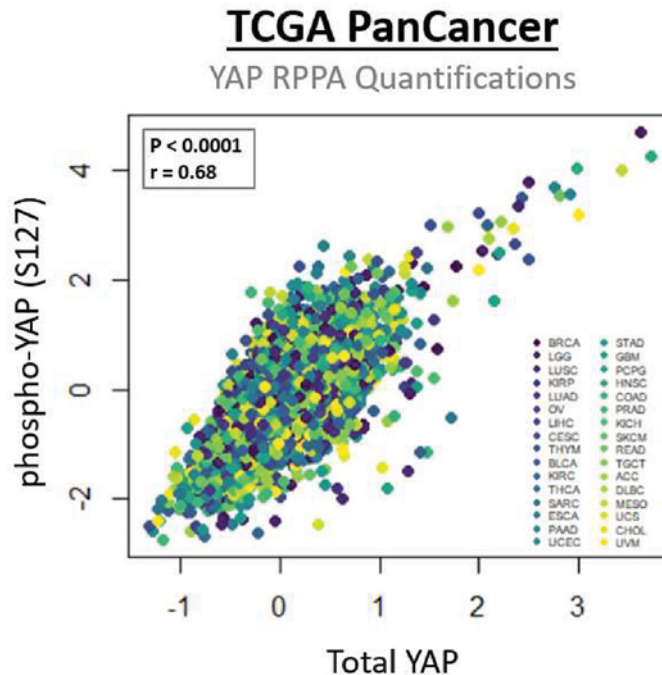


Figure 4. Implementing YAP levels as prognostic indicator of YAP activity

Scatter-plot showing correlation between total YAP levels and levels of pYAP (S127) in patients across a range of cancer types. A strong and significant positive correlation exists between the levels of the two proteins, indicating that in patients with high levels of pYAP (S127), a concurrent increase in total YAP levels is observed. Points shown comprise RPPA data across the pan-cancer dataset (obtained from the Genomic Data Comms portal; <https://gdc.cancer.gov/>), normalised across cancer subtypes (level 4). Correlation coefficients and *P*-values were determined via Spearman method.

development embryogenesis. A notable exception to this is *NF2*, which is mutated in the hereditary condition neurofibromatosis type 2, which causes development of benign schwannoma, meningiomas and ependymomas [49]. In the context of cancer, *NF2* was consequently initially linked to oncogenesis through this association of *NF2* mutations and neurofibromatosis type 2 due to the observed generation of peripheral and central nervous system tumours [50]. Early research in mice suggested that truncation of just one copy of the mouse orthologue, *Nf2* [51], was sufficient to induce a spectrum of different cancer types, including osteosarcoma, lymphoma, lung adenocarcinoma and hepatocellular carcinoma [52]. Since these initial findings, *NF2* has been found to be loss-of-function mutated in ~20–40% pleural mesothelioma (PM) cases [53–56] and 7% of renal cell carcinoma (RCC) patients [57], with a high degree of subtype-specificity noted, as exemplified by the papillary subtype of RCC, which exhibits a mutation frequency of 23% [58]. *NF2* is also infrequently mutated in hepatocellular carcinoma (2%) and intrahepatic cholangiocarcinoma (5%) [59], highlighting *NF2*'s critical role as a tumour suppressor.

NF2 (or Merlin) is an upstream regulator of the core kinase cascade and is activated in response to a variety of cellular stresses, many of which are present during the process of oncogenesis and metastatic niche formation. For example, serum factors such as lysophosphatidic acid (LPA), a phospholipid historically associated with *in vitro* tumorigenesis [60,61], act as activators of YAP/TAZ. This is evidenced by LATS1/2 activation and subsequent YAP and TAZ inactivation on serum starvation in HEK293A and U2OS cells [62,63], a phenomenon mediated by *NF2* [64]. In a similar fashion, *NF2* also partially orchestrates the inactivation of YAP via phosphorylation observed on glucose starvation [64]. *NF2* is a junctional protein and acts as a mediator of contact inhibition, the process by which motility and proliferation are impeded in regions of high cell density. In this capacity, *NF2* is activated via a range of effectors, with *NF2* historically shown to be essential for the formation of adherens junctions, the cell–cell complexes that facilitate adhesion and instigate contact inhibition [65]. Integrins can also activate an RAC/PAK1 axis, which in turn phosphorylates and inactivates *NF2* (at S518), possibly through *NF2*'s function as a scaffold to bring LATS and YAP in close proximity [17], while cell–cell interactions inhibit YAP/TAZ-induced transcription via *NF2*'s regulation of FASN-mediated TEAD palmitoylation [46].

Table 1 Hippo pathway dysregulation and human cancers

Cancer type	Hippo component	Impact in cancer	Evidence
Breast cancer	YAP/TAZ	Nuclear translocation of TAZ is associated with the highly aggressive, triple-negative subtype of breast cancer [305]; YAP and TAZ facilitate stem cell-like properties in cancer cells [297,306]	Immunohistochemical assay of tumour tissue microarray; <i>in vitro</i> and <i>in vivo</i> experimentation
EHE	YAP/TAZ	Widespread fusions of TAZ, with recurrence through infrequent YAP fusions [98–100]	Whole-exome sequencing, cytogenetic analysis of patient samples
Ependymoma and Meningioma	YAP	Subpopulations of patients with YAP fusions [101,102,105]	Methylome characterisation and molecular inversion probe analysis of patient samples
Glioblastoma	YAP/TAZ	Transcriptional regulators of stem-like cell gene programs [145]	scRNA-seq of clinical samples
Hepatocellular carcinoma and Cholangiocarcinoma	YAP	YAP up-regulation leads to drug resistance <i>in vitro</i> [157] and worse prognosis in patients [154]; YAP activity shows contextual tumour suppressive ability, where overexpression in peritumoral hepatocytes leads to tumour clearance [215]	<i>In vitro</i> experiments and qPCR of clinical tissue; immunocompetent mice models
Mesothelioma	NF2, LATS1/2, SAV1	Frequently deleted/loss-of-function mutated in patients [12,54]	Whole-exome sequencing of patient samples
Non-small cell lung cancer (NSCLC)	YAP/TAZ	YAP enriched in nucleus in tumour relative to healthy tissue [307]; YAP and TAZ overexpression correlates to poor survival in NSCLC patients [308,309]; YAP and TAZ maintain stemness in NSCLC cancer cells [310]	Immunofluorescent staining of tumour tissue; immunohistochemical quantification and RNA-seq; <i>in vitro</i> spheroid models of lung cancer
Osteosarcoma	YAP/TAZ	YAP protein levels up-regulated in OS cancer patients [311], with YAP/TAZ staining showing prognostic potential [312]; SOX2-Hippo axis activates YAP, maintaining cancer stem cell populations [148,251]	Immunohistochemistry of patient tumour microarray; <i>in vitro</i> analyses
Pancreatic ductal adenocarcinoma	YAP/TAZ	Associated with the highly aggressive, squamous subtype of PDAC [201,313]	RNA-seq and whole-exome sequencing of patient samples
Prostate cancer	YAP	Facilitates castration-resistant growth and invasiveness [314,315]; up-regulated in CRPC, but down-regulated in NEPC subtypes [210,316]; hydroxylation suppresses cell invasion [209]	<i>In vitro</i> and <i>in vivo</i> experimentation; clinical RNA-seq datasets; cell line analysis
Uveal melanoma	YAP	G $\alpha_{q/11}$ mutant UM cells are dependent on YAP for oncogenic growth [178,317]	<i>In vitro</i> and <i>in vivo</i> experimentation

Non-exhaustive list of cancers in which the Hippo pathway is dysregulated, with a breakdown of the kind of perturbation observed, the pathway component(s) affected, and supporting evidence.

Tumours are known regions of poor nutrient availability due to the metabolic activation inherent to cancer [66], alongside reduced perfusion of metabolites and serum-derived factors [67], therefore the ability to escape an anti-proliferative response to glucose/serum-factor starvation would confer an advantage to NF2-mutant tumour initiators. The potential to proliferate and retain motility within a cell-dense region of tissue would also likely facilitate tumour growth and metastasis on loss of NF2. This, therefore, reinforces the likelihood that NF2 enacts its tumour suppressive role via the ability to act as a sensor of cellular stress and regulate a response to both serum/glucose starvation and contact inhibition.

YAP/TAZ domain organisation and fusion events

YAP and TAZ consist of an N-terminal TEAD-binding domain (TBD), which wraps around the globular structure that defines TEAD proteins, interacting at three distinct interfaces [68,69]. Outside of cancer, mutations in TEAD are present in Sveinsson's chorioretinal atrophy, an autosomal dominant eye disease, which prevents YAP/TAZ-TEAD binding [70–72]. Mutations in residues essential for YAP binding in TEADs were shown to disrupt transformation in MCF10A breast cancer cells and metastasis of a range of cellular model systems *in vivo* [69,73]. A 14-3-3 binding domain sits just downstream of the TBD; this includes the S127 residue, whose phosphorylation status determines 14-3-3 protein binding [74]. YAP and TAZ both contain WW domains, named for two highly evolutionarily conserved tryptophan residues contained within the domain [75]. Of note, there are a number of components within the Hippo signalling kinase cascade that contain PPxY, WW-binding motifs, including LATS1/2 and MST1/2 [76–78]. To explore the potential role of the WW domain in facilitating interactions between core cascade kinases and YAP/TAZ, a study focused on a fragment of the fly YAP orthologue, Yki, lacking a WW domain. Similar to the intact Yki, this

fragment retains the ability to be phosphorylated by Wts, suggesting that this is independent of WW binding to Wts and regulation of Yki phosphorylation [79]. The WW domain in YAP is, however, essential for its activity in order to drive proliferation *in vitro* and *in vivo* [79,80] and can facilitate association between YAP and a variety of transcription factors, such as ERBB4 [81,82], JUNB [83] and RUNX2 [84], suggesting a TEAD-independent role for YAP as a transcriptional co-activator. A total of eight isoforms of YAP have been reported [85], with two major isoform types: YAP1 and YAP2, which contain one and two WW domains respectively [81]. These isoforms are in general functionally similar, however YAP2 has been shown to activate apoptosis in HEK293 cells [86], whereas YAP2L, a variant of YAP2, appears capable of dimerising to enhance oncogenic capacity [87]. The second WW domain associated with YAP2 may also have a functional role, as it has demonstrated potential as an enhancer of YAP's potential as a transcriptional co-activator [81,88]. TAZ encoded by *WWTR1* is also expressed as several isoforms, some of which have markedly different functions [89,90], bringing additional complexities into the Hippo pathway. YAP and TAZ contain a relatively unstructured C-terminal transactivation domain (TAD) [91,92], which facilitate transformation *in vitro*, driving proliferation, migration and invasion [93,94], though is dispensable for anchorage-independent growth *in vitro* [93]. A PDZ-binding domain sits just downstream of the TAD, at the COOH terminus of YAP/TAZ, which is essential for nuclear translocation [95,96]. Evidence demonstrates that the TBD, TAD and PDZ-binding domains are all essential for YAP/TAZ function as a co-activator of TEAD-mediated transcription *in vitro* [88]. Finally, both YAP and TAZ contain relatively high levels of intrinsic disorder spanning across the entirety of the protein structures [97], suggesting a high degree of structural flexibility outside of short, highly conserved domains, may facilitate protein function.

Downstream of the kinase cascade, multiple activating fusions of YAP and TAZ, the transcriptional co-activators of the Hippo pathway, have been documented in a variety of rare cancer variants (Figure 2). An exemplar of this is epithelioid hemangioendothelioma (EHE), a vascular sarcoma that presents in a range of anatomical positions, thus exhibiting a variable prognosis, however with a tendency to metastasise early in its clinical course. This rare cancer-type is characterised by a near ubiquitous translocation resulting in a fusion protein of TAZ-CAMTA1 present in the vast majority (>90%) of patients [98], with an additional, less frequent YAP-TFE3 fusion protein also observed in a subpopulation of those diagnosed with EHE [99,100]. Another fusion example is present in a rare subtype of glioma, supratentorial ependymoma, in which a subset of ~10% of patients exhibit a YAP-MAML1 or a highly infrequent YAP-FAM118B fusion [101,102]. The group of ependymomas with YAP1 fusions occurs predominantly in children [103]. In poroma (benign) and porocarcinoma (malignant) tumours, which arise from sweat glands, YAP-MAML2 and YAP-NUTM1 fusions are present in >80% and ~60% of patients respectively [104,105]. Finally, YAP-MAML2 fusion is also observed in a subset of sporadic NF2 wildtype meningioma, whose methylomes mirror NF2 mutant tumours [106], and has also been reported in nasopharyngeal carcinoma [107].

In both EHE and ependymoma, YAP fusion events drive the transcription of TEAD target genes. To demonstrate this, a mouse model was developed expressing a tamoxifen-inducible knockin of TAZ-CAMTA1, which exhibits human-like EHE with a concurrent enrichment of YAP/TAZ target genes and pathways to a similar degree as in human disease [108]. Additionally, Hippo pathway dysregulation has been shown to result in tumorigenesis similar to that seen in cancer types involving YAP/TAZ fusion proteins, with both expression of constitutively active YAP or KO of LATS1/2 in a subpopulation of neuronal precursor cells in mice resulting in the formation of ependymoma-like tumours and up-regulation of YAP/TAZ target genes [109]. This core involvement of YAP/TAZ fusion proteins and target genes in the transformation of nervous tissue has been probed in more detail via preclinical experimentation, which has shown that cancer cells exhibiting a YAP-MAML2 fusion are dependent on the fusion protein, with loss associated with decreased viability, while also displaying increased expression of YAP/TAZ signature genes [110]. Experiments using HEK293 cells highlight that TADs of YAP-fusion partners are critical in driving the enhanced YAP activity associated with fusions and drive Hippo kinase cascade resistant nuclear localisation [111]. This suggests the substitution of the TAD and PDZ domains of YAP likely facilitates a constitutively nuclear, and hence active, YAP, which may account for the observation that these fusion proteins universally retain the N-terminal TEAD interacting domain, but not the C-terminal part of YAP and TAZ. The regularity of YAP fusion proteins in ependymomas and meningiomas, tumour types associated with neurofibromatosis 2, alongside preliminary findings to suggest exclusivity with NF2 mutation [101,106], is further evidence that Hippo pathway dysregulation is a common driver of oncogenesis in these rare cancer types of the nervous system.

Many of the rare cancer types that exhibit frequent YAP/TAZ fusions are associated with a generally low mutational burden, with supratentorial ependymomas characterised by fusion proteins in just two oncogenes (YAP and RELA) [101,103], while in EHE, <20% of patients exhibit a canonical oncogenic alteration beyond YAP/TAZ fusion [112]. This suggests that these chromosomal rearrangements are capable of transforming cells with relative genomic stability, further reinforcing the oncogenic potential of YAP/TAZ activity. In contrast with this, porocarcinomas generally

display a higher degree of heterogeneity, more in line with most commonly studied cancer types [113], with frequent activation/inactivation of a range of oncogenic/tumour suppressive drivers [114]. However, it is apparent that fusion partners play a role in tumour development, with C-terminal fusion fragments exhibiting frequent conservation of nuclear localisation signal (NLS) and TAD motifs [98,115–118] (Figure 2), as demonstrated by glutamine-rich and highly acidic regions historically associated with TF-binding transactivation domains [119,120]. This is further evidenced by a case of porocarcinoma reported with a BRD3-NUTM1 fusion, independent of YAP rearrangement [121]. Collectively, these findings emphasise directly that YAP and TAZ, in combination with functional fragments of select fusion partners, are essential drivers in a subset of rare cancer varieties, likely in a highly context-specific manner, given the relative absence of YAP/TAZ fusions in cancer types arising from different tissues.

YAP/TAZ activation in cancer

Beyond genomic perturbation of the Hippo components, dysregulation at the transcriptional level is observed across a broad range of cancer types. Both *in vitro* and *in vivo* studies have reinforced YAP and TAZ's role in driving proliferation in cancer cells and tumour tissue, as well as cellular migration, metastasis and resistance to therapeutics [122–124]. YAP drives transcription of integral cell cycle genes, such as the cell cycle transcription factor *FOXM1* and its target *CCND1* (encoding cyclin D1) in PM cells [32]. These pro-proliferative transcriptional programs may be driven in part by YAP/TAZ–TEAD association with the cell cycle transcription factor complex, AP-1. In a variety of cancer cell lines, YAP, TAZ and TEAD are found to colocalise with AP-1 to regulatory elements of the genome and are necessary for AP-1-mediated expression of cell cycle transcriptional programs, driving cancer cell proliferation and tumorigenesis in *in vivo* xenograft models [83,125,126]. Hyperactive YAP/TAZ also provides cells with a metabolic competitive advantage under nutrient-limiting conditions, in part by up-regulating glucose and high-affinity amino acid transporters [127–129]. This is especially relevant in the context of cancer development, where YAP/TAZ-regulated metabolic gene programs likely play critical roles in nutrient-poor environments such as the tumour microenvironment [130,131] and potentially facilitate the metabolic transformation to aerobic glycolysis historically associated with tumorigenesis [132–134]. There is also evidence that this metabolic IQ calmodulin-binding motif shift, often referred to as the 'Warburg Effect' [135], can act to drive YAP/TAZ activation, potentially instantiating a positive feedback loop within the cancer setting [136,137]. Additionally, there is accumulating evidence that YAP/TAZ activity is associated with pro-survival programs and the development of resistance to commonly used therapeutics. As an example, YAP mediates autophagy activation and survival in response to nutrient deprivation in breast cancer cells, likely due to YAP-TEAD-induced gene expression [34]. YAP mediates resistance to RAF and MEK inhibition in a range of cancer types, with a clear synergy between YAP knockdown (KD) and therapeutic inhibition of either BRAF with vemurafenib or MEK with trametinib [33]. Probing the molecular basis of the association between YAP/TAZ and pro-cancerous pathways is therefore a primary focus of recent cancer research.

As YAP/TAZ are key regulators of early developmental processes [138,139], it is not surprising that they frequently act in a pro-oncogenic capacity when not finely regulated, and drive the stemness and plasticity associated with cancer development, including metastasis, infiltration and resistance to therapeutics [140,141]. Epithelial-to-mesenchymal transition (EMT) is a critical step in most types of early oncogenesis, whereby terminally differentiated cells undergo a dedifferentiation, assuming stem-like properties. In Py2Ts, a murine breast cancer cell line proposed as a model to study EMT [142], YAP/TAZ–TEAD interactions are essential in driving EMT and expression of EMT transcriptional programs [143]. In the context of human cancers, YAP/TAZ in some instances act downstream of MEKK3 (or MAP3K3) to maintain stemness in pancreatic cancer cells [144], while collation of single cell RNA-seq (scRNA-seq) datasets from patients with glioblastoma (GBM) revealed that YAP and TAZ drive a regulatory network associated with the GBM stem cell state [145]. YAP/TAZ may in part be driven by a SOX2-Hippo axis; SOX2 is a master transcription factor historically associated with pluripotency and stem cell maintenance [146] and is also often linked to tumorigenesis [147]. This SOX2-Hippo axis has been shown to directly inhibit NF2 and activate YAP, driving cell plasticity in both osteosarcoma and GBM cell lines [148]. YAP/TAZ activity plays a prominent role in early liver development, with multiple studies in zebrafish and mouse showing that repression of the Hippo kinase cascade/hyperactivation of YAP is sufficient to cause overgrowth within the liver and biliary duct [149–153]. YAP is also overexpressed in cholangiocarcinoma, cancer of the biliary duct, with increased expression corresponding with a worse patient outcome [154], in some rare instances due to loss of NF2 function [155,156], while YAP promotes therapeutic resistance in *in vitro* models of hepatocellular carcinoma [157]. This serves to highlight the requirement within cells to finely balance YAP/TAZ activity to promote healthy organogenesis during development and avoid tumorigenesis post-development.

While a range of transcriptional programs have been proposed to act as drivers of oncogenesis downstream of the transcriptional module of the Hippo pathway, it is important to understand how these transcriptional effects are mediated by YAP/TAZ–TEAD while considering potential therapeutic approaches to inhibit these processes. In an NF2 mutated breast cancer cell line model, YAP, TAZ and TEAD were shown to preferentially localise to enhancer elements [125]. These non-coding segments of the genome are typically just several hundred base pairs in length and act in a *cis*-regulatory manner to modulate transcription via the recruitment of transcription factors and transcriptional co-activators [158]. The term super-enhancer was originally conceived to describe key regulators of stem cell transcription programmes in the context of embryonic stem cells [159–161] and are defined as elongated clusters of enhancer regions with increased transcription factor densities, which exhibit an enhanced capacity to drive transcription of select genes [159]. Given their association with embryonic stem cells and the master regulators that drive cellular plasticity, many genes regulated by super-enhancers encode proteins that are essential for development and pluripotency, such as SOX2, Nanog and OCT4 [159,162]. These can be hijacked in cancer cells to promote tumorigenesis, with breast and colorectal cancer cells found to exhibit increased levels of the H3K27Ac mark of epigenetic activation at super-enhancer sites of known oncogenes, such as *c-Myc* and *ESR1* (encoding oestrogen receptor α (ER α)), relative to non-malignant tissue as determined by ChIP-seq [163]. Core Hippo pathway components associate closely with these super-enhancers, with YAP and TAZ populating super-enhancer regions as a result of their association with BRD4, a member of the bromodomain and extraterminal domain (BET) family of epigenetic readers [164]. This interaction mediates the transcription of pro-proliferative genes and is required for cancer cell viability [164]. A model for transcription factor and binding partner capture within super-enhancers has been proposed [165], by which liquid–liquid phase separation (LLPS), whereby a homogenous mixture demixes forming separate condensed and dilute phases, drives the formation of membraneless organelles [166]. This might be of particular relevance to YAP and TAZ, which readily undergo LLPS under specific stimuli, such as upon osmotic challenges, as a result of intrinsic disorder, a phenomenon that drives widespread transcriptional effects within cells [157,167]. For example, YAP forms condensates under conditions of osmotic stress, driving nuclear localisation and transforming chromatin topology, resulting in a clustering of accessible chromatin and the transcription of YAP/TAZ target genes [168]. In contrast with this, TAZ undergoes LLPS at steady-state *in vitro*, suggesting that phase separation is particularly important for TAZ relative to YAP [97]. This LLPS is inhibited by Hippo kinase cascade activation, while TAZ condensates colocalise with TEADs and markers of super-enhancers such as BRD4 and MED1, activating expression of YAP/TAZ target genes [97]. As further evidence, in mice embryonic stem cells, hyperactive Yap induced by Mst1/2 KO is found to phase-separate and colocalise with master transcriptional regulators Sox2, Nanog and Oct4, disrupting stem cell differentiation [169] and highlighting the importance of LLPS in coordinating association between YAP/TAZ and super-enhancer elements.

The role of G protein-coupled receptor signalling in regulating the Hippo pathway in cancer

G protein-coupled receptors (GPCRs) are transmembrane proteins capable of binding a diverse set of ligands [170], facilitating the response to a range of extracellular stimuli and inducing various signalling cascades via the activation of G proteins. G proteins function in signal transduction as GTPases, acting via the hydrolysis of GTP to GDP, and comprise two major families: monomeric small GTPases [171] and heterotrimeric G proteins that consist of α , β and γ subunits. Within the heterotrimeric G protein family, the G α subunit is the primary functional element required for GDP/GTP binding and decides G protein nomenclature [172], with multiple subfamilies of G protein α -subunits including G $\alpha_{12/13}$, G $\alpha_{q/11}$ and G α_s . GPCRs activate G proteins by inducing exchange of GDP for GTP, a process mediated by guanine nucleotide exchange factors [173]. Both GPCRs and G proteins are frequently mutated across a vast variety of cancer types, with GPCR, G $\alpha_{q/11}$ and G α_s mutations present in ~20, 4 and 6% of all human cancers [174], while recent work has suggested that G protein disruption may be even more common than previously observed when mutually exclusive mutations across G protein families are considered [175]. GPCRs and coupled G proteins differentially regulate the core kinases of the Hippo signalling pathway, with YAP found to be activated by serum constituents such as the bioactive signalling lipids LPA and sphingosine 1-phosphate (S1P), but inhibited by metabolic stress hormones [62]. These effects are mediated by the kinases of the Hippo pathway, with LATS1/2 inhibited by G $\alpha_{12/13}$ and G $\alpha_{q/11}$ subfamilies and activated by the G α_s subfamily of heterotrimeric G proteins [62]. To explore the role of G proteins in regulating YAP/TAZ in the context of cancer, the role of activating G $\alpha_{q/11}$ mutations, which occur frequently in uveal melanoma (UM) [176,177], in driving YAP-mediated oncogenic processes was examined in UM cell lines. UM cells with mutations in *GNAQ* or *GNA11*, which encode G $\alpha_{q/11}$ proteins, demonstrate increased YAP activity, while ectopic expression of mutant G $\alpha_{q/11}$ also induce YAP activation in HEK293 cells [178]. This is of

particular relevance, given that $G\alpha_{q/11}$ mutations enhanced susceptibility to YAP-TEAD inhibition via treatment with the YAP-TEAD inhibitor verteporfin *in vitro* [178], suggesting that cancers driven by these G protein subfamilies, as well as GPCRs that regulate them, may be vulnerable to therapeutic targeting of Hippo pathway effectors.

Downstream of heterotrimeric G proteins, small GTPases, in particular RhoA, a member of the Ras superfamily Rho GTPases, are also known to regulate Hippo pathway activity. The family of LPA-activated GPCRs activate Rho-dependent signalling in response to LPA and absence of mechanical force [179,180], an axis which, when active, inhibits LATS1/2 [62]. This phenomenon, instigated by $G\alpha_{12/13}$, utilises the upstream mechanosensory component of the Hippo pathway [2], with activated RhoA driving F-actin assembly and leading to LATS1/2 inactivation [181]. Recently, super-resolution dSTORM imaging further resolved this process, highlighting how YAP activity is inhibited in response to cell contact and mechanotransduction via RhoA repression [182]. These observations point to the importance of RhoA as a mediator of GPCR regulation of Hippo signalling, which is of particular relevance in cancer given RhoA plays a key role in transformation induced by aberrant GPCR signalling [183]. Across a range of cancer types, *RHOA* overexpression is associated with oncogenesis, in patients and cell line models, as well as advanced disease [184–187], further highlighting its role in progression of cancer. The involvement of RhoA in oncogenesis may be in part due to its ability to restructure the actin cytoskeleton and drive motility, as oncogene-mediated RhoA activation induces cancer cell migration and invasion [188,189]. However, recent *in vitro* and *in vivo* experiments have shown that YAP further mediates the oncogenic potential of RhoA, driving the expression of downstream transcriptional programs that induce restructuring of the cytoskeleton and extracellular matrix, enhancing cancer cell invasion [190,191], while LPA-mediated RhoA activation and subsequent dephosphorylation of YAP induce migration in ovarian cancer cells [192].

The oncogenic Kaposi sarcoma-associated herpesvirus (KSAH), a virus responsible for the initiation of Kaposi sarcoma, generally in immunocompromised patients such as those with an advanced HIV infection, depends on a viral GPCR (vGPCR) element to induce tumorigenesis [193]. Tumorigenesis induced by vGPCR is mediated by and dependent on the Hippo pathway *in vitro*, with vGPCR inhibiting LATS1/2 through $G_{12/13}$, $G\alpha_{q/11}$ and RhoA, leading to increased activation of YAP/TAZ and enhanced proliferation and migration [194]. It is also worth noting that there are a number of members of the Ras subfamily of GTPases which are frequently mutated in human cancers, including HRAS, NRAS and most commonly, KRAS, with activating Ras mutations found in ~20% of cancer patients [195,196]. YAP/TAZ facilitate tumorigenesis in Ras-driven cancers [188,189], possibly via regulation of overlapping, downstream transcriptional targets [197], and can act as a surrogate for oncogenic Ras *in vitro* when KRAS is suppressed in cell lines from a range of cancer types [198]. This is particularly relevant in pancreatic ductal adenocarcinoma (PDAC), in which the aggressive squamous subtype exhibit independence of oncogenic KRAS [199], a near constitutive driver of PDAC [200]. *YAP1* expression levels are associated with poor patient outcome and the squamous subtype in PDAC [201,202], with YAP acting to bypass KRAS dependency in pancreatic cancer cell lines [201], suggesting an ability to induce transcription of targets up-regulated on aberrant KRAS signalling. Collectively, this work reinforces the role of YAP/TAZ as important effectors of oncogenic GPCR, G protein and general GTPase signalling.

YAP/TAZ as tumour suppressors

Despite the clear role YAP/TAZ play in tumorigenesis, some studies have linked their activity to anti-cancer pathways in a variety of cancer types. For example, low levels of *YAP1* expression have been associated with a significantly poorer prognosis in haematological cancers, with *in vitro*-based research highlighting the role YAP plays in reducing proliferation in multiple myeloma cells [203], likely mediated via interaction between YAP and the pro-apoptotic p73 [204]. Similarly, in small cell lung cancers (SCLCs), *YAP1* is minimally expressed or even absent from most cases, particularly those of neuroendocrine lineage, with just a subpopulation of patients displaying high levels of expression [205]. Loss of heterozygosity in chromosome 11q22–q23, the region containing *YAP1*, has historically been observed in breast cancer [206], while YAP knockout or KD in a variety of breast cancer cell lines yields a reduction in tumorigenic potential, as determined by capacity for anchorage-independent growth, migration, and ability to form xenografts in mice [207,208]. A recent study highlights that cell lines originating from multiple tissues of origin exhibited an increase in *in vitro* metastatic potential after KD of *YAP1*, further suggesting a tumour suppressive role; however, this suppressive phenotype was only observed when YAP was hydroxylated in a prostate cancer cell line [209]. These observations are surprising, given that YAP has typically been found to drive cell proliferation and oncogenesis in prostate cancer [141]. There is however a subset of neuroendocrine prostate cancers exhibiting a silencing of YAP [210], suggesting that YAP/TAZ may exhibit a context-dependent tumour suppressive function via post-translational modification. Importantly, a range of these studies exclusively focus on YAP, and therefore TAZ

Table 2 Inhibitors of YAP/TAZ activity

Compound name	Mechanism of action	Clinical viability
Verteporfin	Disrupts YAP–TEAD association [217], possibly partly via cytoplasmic sequestration of YAP [318]	Approved for clinical use and historically used as non-cancer therapeutic [216]; however, YAP/TAZ independent anti-cancer potential and cell death reported <i>in vitro</i> [218,219]
CA3	Reduces expression of <i>YAP1</i> , as well as YAP–TEAD transcriptional activity [319]	No clinical data, however anti-cancer potential is validated <i>in vivo</i> [320,321]
Cyclic YAP-like peptides	Acts as a competitive inhibitor of intact YAP, disrupting YAP–TEAD interaction [322]	Peptides are non-cell permeable and therefore require additional intracellular delivery tools before being used clinically [322]
Super-TDU	Mimics the structure of the TDU domain of VGLL4, found to competitively bind TEAD, acting to disrupt the YAP–TEAD interaction [323]	No clinical data; however, a variety of similar acting compounds have recently been patented [324] and are viable for testing
Flufenamic acid	Binds the central, hydrophobic pocket of TEADs, disrupting YAP–TEAD transcriptional activity; however, YAP–TEAD binding is maintained [325]	Approved for clinical use as non-steroidal anti-inflammatory drug (NSAID) [326], however no clinical data on anti-cancer potential
TED-347	Flufenamic acid derived molecule that binds TEAD palmitate pocket, displacing YAP and inhibiting YAP–TEAD transcriptional activity [221]	No clinical data, though likely similar pharmacological profile to flufenamic acid
Various palmitoylation inhibitors	A selection of small molecule inhibitors have been recently identified that bind the palmitoylation pocket of TEAD, acting as a dominant-negative inhibitor of YAP/TAZ activity [223–225]	No clinical use data, as compounds are in early stages of development/testing, with clinical trials currently recruiting (NCT04665206)

List of therapeutics developed to target the transcriptional module of the Hippo pathway, with corresponding mechanism of action and potential to reposition clinically.

compensatory roles [211,212] might not be picked up. Consequently, both TAZ and YAP function and activity are critical to evaluate in order to obtain firm conclusions.

Recently, a transcriptional profile for cancers that exhibit YAP silencing showed a binary switch from YAP dependency to independency apparent across pan-cancer datasets. The present study revealed that YAP and TAZ act as tumour suppressors selectively in retinoblastomas and SCLCs exhibiting loss of the *RB1* gene, which is mutated in the vast majority of both cancer types [205,213]. Probing cell line and clinical transcriptomes revealed the existence of multiple clusters of cancers; a relatively small subpopulation of cancer types in which YAP/TAZ are silenced, constituting haematological malignancies and small cell neuroendocrine cancers, and the majority of those in which YAP/TAZ are actively expressed, primarily consisting of solid, non-neuroendocrine tumours [214]. To compound the idea of YAP/TAZ acting as tumour suppressors or oncogenes in this binary fashion, a recent study leveraged mice models of cholangiocarcinoma and hepatocellular carcinoma to study the impact of YAP/TAZ dysregulation in peritumoral immune cells. This showed that hyperactivation of YAP in tumour cells promotes cancer progression, while in surrounding hepatocytes, YAP/TAZ hyperactivity leads to tumour suppression [215]. These results highlight the nuanced and contextual role the Hippo pathway plays in tumour development, although a majority of cancers clearly exhibit some dependence on YAP/TAZ transcriptional activation.

Therapeutics and Hippo signalling

Direct targeting of YAP/TAZ-TEAD

Early attempts to target YAP/TAZ activity focused on disrupting YAP/TAZ-TEAD binding, with the first compound to efficiently inhibit this interaction discovered by using a YAP-TEAD luciferase reporter assay. This approach identified verteporfin, a Food and Drug Administration (FDA)-approved member of the porphyrin family historically used as a photosensitiser to treat macular degeneration [216], to also act as an inhibitor of YAP–TEAD transcription, which selectively inhibited tumour growth in murine models of YAP-driven hepatocellular carcinoma [217]. However, the clinical potential of verteporfin in targeting YAP-TEAD driven cancers is limited as off-target effects have been reported, the cytotoxicity associated with verteporfin treatment having been shown as acting independently of YAP inhibition in a range of cancer cell models [218,219]. This has led to more recent efforts to develop allosteric inhibitors that disrupt the YAP–TEAD interaction, with a variety of compounds having been shown to exhibit potential [220–222] (Table 2), though future studies are required to validate specificity before clinical efficacy can be considered.

As previously discussed, TEAD activity is dependent on palmitoylation [45–47], a phenomenon that can be targeted molecularly. To this end, a variety of TEAD inhibitors have been developed that target palmitoylation sites

conserved across TEAD isoforms, inducing a dominant-negative effect on transcriptional regulation [47,223]. The anti-cancer potential of this therapeutic approach has been validated in a mesothelioma xenograft model, in which NF2-deficient cancer cells exhibited sensitivity to inhibition of TEAD palmitoylation [224]. While these broad-acting TEAD inhibitors are currently under development with the intention to reposition to clinical testing in the near future, isoform-specific inhibitors are also being considered as potential tools for research. This is exemplified by the design of a selective inhibitor of TEAD3 [225], whose function is relatively unknown in the context of cancer progression, relative to the other TEAD isoforms [226–228]. Additionally, MST1/2 inhibitors have been developed, with the intention to utilise these to therapeutically stimulate tissue repair and regeneration [229]. However, as a subset of cancers exist in which YAP/TAZ act as putative tumour suppressors [205,210,214], there is a possibility that these cancers may be vulnerable to inhibition of the core Hippo kinase cascade; this approach would however require validation and caution, as MST1/2 classically act as tumour suppressors [230–232].

Strikingly, there is a distinct lack of inhibitors that target YAP or TAZ directly; to evaluate why this is the case, it is necessary to consider protein structure. YAP and TAZ are intrinsically disordered, suggesting a high degree of structural flexibility [97]. Recent advances in deep learning have facilitated *in silico* protein prediction such that current modelling approaches have demonstrated accurate prediction of protein structure to near experimental quality [233]. Implementing this methodology, AlphaFold predictions validate the extent of disorder inherent to YAP and TAZ (Figure 3), with just WW and CC domains predicted with high confidence, along with a small subsection of the TEAD-binding domain. This acts as an indicator that there may be few regions within YAP and TAZ that are susceptible to therapeutic inhibition, as development of small molecule inhibitors will be limited to those select structures within the proteins with a high degree of order. There are also difficulties inherent to inhibition of YAP/TAZ activity via targeting upstream regulatory elements, as this would necessitate the therapeutic activation of the Hippo kinase module. Historically, kinase inhibitors represent a major subfamily of anti-cancer compounds, with a variety of therapeutic avenues involving kinase inhibition showing clinical efficacy in the context of cancer [234,235]. As the majority of kinases involved in cancer act in a pro-oncogenic capacity, there are limited therapeutic options available in terms of activators of kinases, meaning novel compounds would need to be developed to this end. However, there are some clinically viable kinase activators available, as exemplified by compounds known to activate AMP-activated kinase (AMPK), an important sensor of metabolic stress in cells [236]. A variety of therapeutics, including metformin, a drug widely used to treat diabetes [237], induce activation of AMPK [238], some of which have shown anti-cancer potential in preclinical models of various cancer types [239–241], acting as proof that a therapeutic option to switch on the core kinase cascade of the Hippo pathway is viable. Approaches targeting YAP/TAZ protein stability, mRNA levels and translation are alternative approaches that might be productive.

Indirect targeting of YAP/TAZ and associated pathways

Beyond directly targeting the components within the Hippo pathway, an alternative approach may be to indirectly inhibit Hippo pathway effectors via upstream regulators. An attractive example of this may be to inhibit GPCRs associated with G_{12/13} and G_{q/11} subfamilies of G proteins, which activate YAP/TAZ [62,178]. Many drugs commonly used for the treatment of a variety of diseases and conditions interact with GPCRs or proteins associated with GPCRs, with 35% of compounds listed as approved by the United States FDA targeting GPCRs [242]. However, very few of these are utilised specifically within the context of cancer as anti-tumorigenic agents [243], with recent work serving to highlight the potential in GPCR inhibitor discovery and repositioning in cancer [244]. Additionally, G_{q/11} activating mutations have been found to modulate YAP/TAZ activity via focal adhesion kinase (FAK), highlighting potential in inhibition of FAK as a cancer therapy, with *in vitro* validation in UM cell lines [245]. This therapeutic approach is validated experimentally, as NF2 expression levels predict efficacy of FAK inhibition in cells derived from pancreatic cancer patients [246]. Additionally, an improved response is observed with NF2 KD *in vitro* and *in vivo* [246], suggesting that YAP/TAZ activity likely positively correlates with sensitivity to FAK inhibition, given NF2's function as an activator of the Hippo kinase cascade (Figure 1).

An alternative approach is to target the super-enhancer elements that coordinate regulation of expression directly with YAP/TAZ to inhibit the activation of transcriptional programmes involved in tumorigenesis. This approach appears effective in preclinical experiments, with BRD repression via treatment with JQ1, a broad-acting BET inhibitor [247], and BRD2/3/4 KD showing anti-cancer potential *in vivo* models of YAP/TAZ-addicted breast cancer [164]. This treatment strategy has additionally been validated across a range of cancer types [248,249], reinforcing its potential as a therapeutic for the treatment of cancer. Additionally, a mechanism by which the stemness of osteosarcoma cells dependent on the SOX2-YAP axis can be exploited to therapeutically induce adipogenesis has been proposed. In this manner, stem-like tumour cells can be treated with thiazolidinediones, which function as agonists

of PPAR γ , a key transcription factor and nutrient sensor which drives adipogenesis when activated [250]. Adipogenic differentiation in stem cell-like cancer cells stimulated by PPAR γ activation in this manner has been shown to limit tumorigenicity *in vitro* and *in vivo* [251]. Targeting transcriptional targets of YAP/TAZ–TEAD is yet an additional approach; however, since YAP/TAZ regulates hundreds of genes [12,164,252], this is challenging, but might be a feasible context-dependent complimentary strategy.

In liver and prostate cancer mice cell models, hyperactive YAP recruits macrophages [253] and myeloid-derived suppressor cells (MDSCs) [254] respectively, in both cases acting with TEAD to initiate the expression of immunosuppressive cytokines such as CXCL5, CXCL1/2 and CCL2, repressing the immune response. Mouse models of PDAC have further validated this observation, showing that Yap deletion inhibits MDSC recruitment and polarisation, likely via inhibition of Yap–Tead target gene expression [255], a phenomenon that leads to T-cell reactivation and tissue regeneration [255]. Both YAP and TAZ can also drive the expression of programmed cell death 1 ligand (PDL1) [256,257], which binds to and activates PD1, an immune checkpoint receptor that acts to suppress the immune response [258,259]. These observations are relevant in the context of tumour initiation, as immunosuppression is often employed by cancer cells throughout tumorigenesis to evade and survive the immune response, while there has been a concerted effort throughout the past decade to position checkpoint inhibitors to combat this in a clinical setting [260]. This clear role of YAP/TAZ–TEAD in driving the tumour cell intrinsic signals necessary for the oncogenic immunosuppressive phenotype suggests the potential in targeting YAP/TAZ in combination with checkpoint inhibition [13], an experimental approach validated preclinically [261]. This discovery is of particular relevance currently given the recent focus on leveraging immunotherapy to manage a wide variety of cancer types [262,263], with a combinatorial approach that simultaneously targets YAP/TAZ activity potentially overcoming the resistance associated with immunotherapy [264,265]. Noteworthy, enforced expression of constitutively activated YAP/TAZ in a range of tissue culture and cancer cells regularly induces expression of inflammatory cytokines [83,266–270], which directly highlights that the Hippo pathway is likely a cellular nexus that links epithelial, fibroblasts and endothelial inflammatory responses and proliferation during cancer onset and development [13,261,266].

In contrast, LATS1/2 knockout across multiple types of cancer cells in xenograft studies stimulates the anti-cancer immune response via release of nucleic acid-rich extracellular vesicles [271–273]. LATS1/2 loss in these studies [271] enhances tumour immunogenicity, which promotes anti-tumour immune responses and tumour regression leading to a reduction in tumorigenicity *in vivo* [271], suggesting that the Hippo pathway plays a complex role in the involvement of the immune response to oncogenesis. Overall, the context-dependent role the Hippo pathway plays in immune oncology warrants further examination in order to uncover the interplay and complexities between Hippo pathway components and the immune system [274].

Future targeting of Hippo signalling in cancer

Given the relatively recent emergence of the Hippo pathway's role as a cancer driver, much has been learned as to how YAP/TAZ regulates cancer initiation and downstream oncogenic processes, as well as how they are in turn regulated by the upstream, generally tumour suppressive kinase module. This progress has given rise to a concerted effort to develop therapeutics that target components within the Hippo signalling pathway [140,275,276], as highlighted by the recent arrival of a variety of promising TEAD inhibitors, one of which [224] is currently undergoing testing in an actively recruiting clinical trial involving patients with PM (NCT04665206). These therapeutics are of particular importance given the widespread association of YAP/TAZ activity with cancer progression and the pre-clinical evidence supporting the potential of inhibition of YAP/TAZ–TEAD driven expression in suppressing cancer growth. Beyond considering single-agent treatment with a YAP/TAZ/TEAD inhibitor, positioning such therapeutics alongside standard-of-care treatments may present an optimal choice, given the role of downstream Hippo pathway signalling in driving resistance to a variety of anti-cancer drugs [265]. There is additional potential in targeting cancer cells dependent on YAP/TAZ by indirectly targeting the Hippo pathway, disrupting regulation of upstream or downstream components such as GPCR or super-enhancer components, respectively [277–279]. A variety of such strategies involving the targeting of YAP/TAZ activity have been described in the past, including the leveraging of approved, clinically established drugs such as the AMPK agonist metformin and the statin family of HMG-CoA reductase (HMGCR) inhibitors, classically used to treat hypercholesterolaemia. These compounds disrupt YAP/TAZ activity via metformin-induced activation of AMPK [238] and subsequent direct and indirect phosphorylation of YAP [280,281], as well as the disruption of the mevalonate pathway by statins [282], which results in inhibited geranylgeranylation of RhoA and its displacement from the cell membrane, leading to LATS1/2- and MST1/2-independent YAP phosphorylation [283,284]. Recent retrospective analyses of clinical trials have highlighted the anti-cancer potential of these therapeutics [285,286], though these findings should be taken with caution as prospective trials are necessary

to robustly confirm findings [287]. Despite the promise of targeting YAP/TAZ addiction across a broad range of cancer types, there exists the potential that tumour cells may switch from YAP/TAZ dependency to escape therapeutic sensitivity. This is reinforced by the observation that prostate adenocarcinoma cells lose YAP/TAZ expression as they transition to the more aggressive neuroendocrine subtype [214]. These considerations must therefore be taken into account when testing clinical efficacy of next-generation inhibitors.

From a prognostic perspective, the detection of high levels of YAP/TAZ transcriptional activity is generally a uniform indicator of reduced overall survival in patients across cohorts of multiple cancer types, further highlighting the need for therapeutics that target YAP/TAZ addiction in cancer. To exemplify this association between enhanced YAP/TAZ activity and cancer prognosis, a significant decrease in survival time is observed in patients across a variety of The Cancer Genome Atlas (TCGA) cohorts that exhibit an above median average expression of *bona fide* downstream targets of YAP/TAZ [12]. High levels of nuclear YAP also correlate with poor clinical outcomes in a variety of cancers [122,123] and is observed in 70% of PM patients [288]. However, determining YAP/TAZ activity is not always a simple task, partially due to the complex nature of Hippo pathway regulation. There are a variety of players involved in activating and inactivating the core kinase cascade that constitutes the pathway, many of which are complex in cancer development. For example, EGFR, which is frequently mutated to a constitutively active form in lung and breast cancer [289,290], phosphorylates and represses MOB1, inactivating LATS1/2 and resulting in hyperactive YAP/TAZ [291].

Beyond the complex interplay between canonical cancer drivers and the Hippo pathway, further difficulties lie in determining a single prognostic indicator for YAP/TAZ activity from patient biopsies. Conventionally, expression of YAP/TAZ at the transcriptional and protein levels have been interpreted as a metric for activity, which fails to fully account for the nuance in regulation of YAP/TAZ at the post-transcriptional and post-translational levels. As an example of this, quantification of levels of YAP phosphorylated at serine residue 127 (pYAP (S127)) are frequently utilised as a measure of Hippo kinase cascade activity, both in preclinical and clinical cancer samples [292–294]; however, within TCGA reverse-phase protein array (RPPA) datasets, which show quantification of protein levels within patient samples, there is a striking positive correlation between levels of pYAP (S127) and total YAP (Figure 4). This suggests that in patient samples with high levels of YAP phosphorylation at S127, there may be a pool of compensatory, non-phosphorylated and active YAP, indicating that quantification of phospho-YAP alone may be insufficient to determine activity. Another limitation in many studies is the over-reliance on S127 phosphorylation as a sole marker of YAP activity. When initially described in the context of cancer, phosphorylation at S381 was also found to inhibit *in vitro* transformation [37], while cyclin-dependent kinase 1 (CDK1), a key driver of mitosis, phosphorylates YAP at three alternative residues, positively regulating oncogenesis *in vitro* [295]. Collectively, this suggests the need for a biologically meaningful metric of YAP/TAZ activity that fully accounts for the various mechanisms that regulate activity, with quantification of *bona fide* downstream targets perhaps representing an ideal approach [12].

There are many outstanding questions as to the function of the Hippo pathway in the context of cancer. For example, the extent of the functional distinction between YAP and TAZ, the two primary downstream effectors of the pathway. Most research discussed throughout displays a clear focus on YAP, which has been functionally characterised to a far greater extent than TAZ. However, this general focus on YAP is not necessarily reflective of the importance each component plays in signalling. There is evidence to suggest that both YAP and TAZ are regulated similarly in response to a variety of stresses across a range of cellular *in vitro* models such as HEK293A cells [296], suggesting some degree of functional redundancy, while YAP disruption has a greater effect on transcription as compared with TAZ [125]. In contrast, the degree of evolutionary conservation of TAZ within vertebrates [14] suggests some potential functional divergence, while research has validated a non-redundancy in functionality between YAP and TAZ [91]. Within the context of cancer, TAZ plays an important role independent of YAP, particularly in driving cancer stem cell properties, as has been observed in a variety of *in vitro* cancer cell models [297–299]. TAZ, in some instances acts as an upstream effector of the master transcriptional regulator of stemness, SOX2 [300], in contrast with YAP which is directly regulated by SOX2 [148]. This deviation in functionality means some caution must be exercised when interpreting *in vitro* experiments that focus solely on YAP; for example, where YAP's role as a tumour suppressor in cancer cells has been observed and validated via KD, it is possible that TAZ may have acted to compensate for loss of YAP via hyperactivation or increase expression, a phenomenon that has been observed *in vitro* and *in vivo* in the past [296,301,302].

Multiple types and levels of cellular regulatory feedback are prominent features centring on Hippo signalling, tightly and dynamically regulating this potent signalling pathway [3,15]. It is possible that, if parts of these integrations are offset due to mutations or epigenetic silencing in prominent signalling nodes outside the core Hippo pathway machinery, or mechanochemical alterations within the cellular niche, that this might impose unregulated hyperactive YAP/TAZ, causing cancer. There is additionally evidence that various upstream components of the Hippo pathway

can act independently of the downstream transcriptional module, with NF2 exhibiting pleiotropy in mesothelioma [303] and LATS1/2 acting as a regulator of ER α stability in breast cancer cells independent of kinase activity [304]. The upstream regulatory kinase cascade (Figure 1) also undoubtedly have a range of additional substrates that likely feedback and integrate into the Hippo pathway [1,3]. Collectively, the findings discussed herein highlight the need to develop our understanding of this complex signalling pathway as it relates to cancer progression and development, elucidate further the upstream regulatory elements, and disentangle the nuanced context-dependent ability of components to act as tumour suppressors and oncogenes. In so doing, we can more effectively consider stratifying patients according to Hippo pathway dysregulation and develop therapeutic options for clinical management of YAP/TAZ-driven cancers.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

AMPK, AMP-activated kinase; BET, bromodomain and extraterminal domain; CDK1, cyclin dependent kinase 1; EHE, epithelioid hemangioendothelioma; EMT, epithelial-to-mesenchymal transition; ER α , oestrogen receptor α ; FAK, focal adhesion kinase; FDA, Food and Drug Administration; GBM, glioblastoma; GPCR, G protein-coupled receptor; HMGCR, HMG-CoA Reductase; KD, knockdown; LLPS, liquid–liquid phase separation; LPA, lysophosphatidic acid; MAP4K, mitogen-activated kinase kinase kinase; MDSC, myeloid-derived suppressor cell; NLS, nuclear localisation signal; PDAC, pancreatic ductal adenocarcinoma; PM, pleural mesothelioma; PP2A, protein phosphatase 2; RCC, renal cell carcinoma; SCLC, small cell lung cancer; STK25, serine threonine kinase 25; STRIPAK, striatin-interacting phosphatase and kinase; TAD, transactivation domain; TBD, TEAD-binding domain; TCGA, The Cancer Genome Atlas; UM, uveal melanoma; vGPCR, viral GPCR.

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