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YAP1 and its fusion proteins in cancer initiation, progression and therapeutic resistance

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Abstract

YAP1 is a transcriptional co-activator whose activity is controlled by the Hippo signaling pathway. In addition to important functions in normal tissue homeostasis and regeneration, YAP1 has also prominent functions in cancer initiation, aggressiveness, metastasis, and therapy resistance. In this review we are discussing the molecular functions of YAP1 and its roles in cancer, with a focus on the different mechanisms of de-regulation of YAP1 activity in human cancers, including inactivation of upstream Hippo pathway tumor suppressors, regulation by intersecting pathways, miRNAs, and viral oncogenes. We are also discussing new findings on the function and biology of the recently identified family of YAP1 gene fusions, that constitute a new type of activating mutation of YAP1 and that are the likely oncogenic drivers in several subtypes of human cancers. Lastly, we also discuss different strategies of therapeutic inhibition of YAP1 functions.

Keywords

YAP1; Gene fusions; YAP1 fusion; Cancer; Hippo signaling pathway

Introduction

The Hippo Signaling Pathway is a key regulator of cell growth, tissue homeostasis, and organ size. It can be divided into a tumor suppressive upstream core kinase cascade (including the serine/threonine kinases MST1/2 and LATS1/2) that phosphorylates and inhibits the activity of the downstream effector proteins YAP1 (also known as YAP) and TAZ (also known as WWTR1), two transcriptional activators that interact with a series of transcription factors, most notably TEADs. While it is believed that YAP1 and TAZ have similar functions and are both implicated in development and cancer, since the majority of

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research efforts in this area concentrated on YAP1, this review will predominantly focus on YAP1.

YAP1 is a potent transcriptional co-activator that has essential functions in development, stem cell maintenance, normal tissue homeostasis and regeneration. Deregulation and constitutive activation of YAP1 is implicated in cancer initiation, progression, invasion, and therapy resistance, functions that are mostly attributed to a pro-survival and pro-proliferative transcriptional program elicited via its interaction with TEAD transcription factors. Elevated nuclear YAP1 staining can be detected in many cancers. The causes responsible for YAP1 activation in these tumors are versatile and include loss-of-function mutations in core Hippo pathway upstream regulators, such as LATS1/2, MST1/2, NF2, or mutations in genes encoding proteins that can impact the core Hippo signaling pathway, such as G protein-coupled receptors or viral proteins. By contrast, activating point mutations in the *YAP1* coding sequence are rare. Recent whole genome sequencing studies have identified several recurrent YAP1 gene fusion events in various cancer types. These YAP1 gene fusions are oncogenic when expressed in mice and constitute the likely tumor-initiating events and oncogenic drivers in the cancers in which they are found.

In this review we will highlight the oncogenic functions of YAP1 and discuss the different mechanisms responsible for de-regulation of YAP1 activity in human cancers with a specific emphasis on the recently discovered role and mechanisms of YAP1 fusion proteins.

Linking YAP1 to the Hippo signaling pathway

YAP1 was initially identified as an interaction partner of the SRC family member YES, hence its name YES-associated protein 1 (Sudol 1994; Sudol et al. 1995b). Subsequently, YAP1 was identified as a transcriptional co-activator that does not directly bind DNA itself but rather functions via the interaction with several transcription factors (Yagi et al. 1999; Strano et al. 2001; Ferrigno et al. 2002; Komuro et al. 2003; Omerovic et al. 2004). At that time, the role of YAP1 as the principle effector of the Hippo signaling pathway remained unknown. Independently from these findings, the function of the Hippo signaling pathway, as well as its role in regulating organ size during development in Drosophila melanogaster was unraveled by a series of studies that identified the critical members of its core kinase cascade Wts, Hpo, Salvador/Sav, and Mats. These works demonstrated that these genes were working in the same signaling pathway and mutations in these genes resulted in organ overgrowth and a “big-headed” phenotype (resembling Hippos) (Justice et al. 1995; Xu et al. 1995; Tapon et al. 2002; Harvey et al. 2003; Jia et al. 2003; Udan et al. 2003; Wu et al. 2003). The newly identified pathway negatively regulating the growth of Drosophila organs during normal development was named Hippo signaling pathway. Further studies showed that the core Hippo pathway genes are highly conserved between Drosophila and mammals and the expression of LATS1 (mammalian orthologue of Drosophila Wts) was able to rescue the phenotype of Drosophila *wts* mutants (Tao et al. 1999). However, the actual effector protein of the Hippo pathway remained unknown until Huang and co-authors identified YAP1 and its Drosophila orthologue Yorkie as the principle effectors of the Hippo signaling pathway and demonstrated that YAP1 is inactivated by the Hippo pathway core kinase cascade via direct phosphorylation by LATS/Wts (Huang et al. 2005). Overexpression of

Yorkie during fly development lead to tissue overgrowth that resembled the phenotypes observed by inactivation of the Hippo core kinase members Hpo, Sav, or Wts, whereas deletion of Yorkie in eye disc cells lead to smaller eyes. Interestingly, overexpression of human YAP1 was able to rescue the effect of Drosophila Hippo pathway hyperactivation, suggesting a strong evolutionary conservation and importance of the Hippo signaling (Huang et al. 2005).

YAP1 functions in normal tissues and cancer

YAP1 has important functions in both normal tissue development, homeostasis, and regeneration. Drosophila melanogaster *Yorkie* (*yki*) null mutants are homozygous lethal and die as late embryos and early first instar larvae; moreover, targeted deletion of Yorkie in eye disc cells results in a significantly reduced organ size (Huang et al. 2005). Similarly, homozygous deletion of *Yap1* in mice is also embryonically lethal, as early as E8.5, due to severe developmental defects (Morin-Kensicki et al. 2006). Conversely, deletion of the Hippo pathway tumor suppressors *Stk3/4* (also known as Mst1/2) and *Sav1* (also known as Ww45) leads to hypoplasia, immature differentiation and embryonic death, whereas targeted deletion of these genes in several organs leads to organ overgrowth due to de-regulated YAP1 activation (reviewed in (Zhao et al. 2010a)). Taken together, these results highlight the important roles of YAP1/Yorkie proteins during normal development. In addition, several studies have highlighted a role for YAP1 and the Hippo Pathway in the regeneration of intestine, skin, liver, heart, and nervous tissues following injury and damage (reviewed in (Wang et al. 2017)). Overall, during normal tissue homeostasis, the Hippo pathway suppresses YAP1 function to maintain stem cell quiescence, but is inhibited upon injury, resulting in YAP1 de-repression and activation to promote stem cell self-renewal and generation of new cells necessary for tissue repair. YAP1 interacts with several signaling pathways, including Wnt signaling, BMP and TGFbeta signaling, as well as EGF and HGF signaling, to promote cell proliferation and in some cases differentiation (Wang et al. 2017).

In addition to its role in normal tissue development and homeostasis, YAP1 has also been shown to play important roles in cancers, where it can act as either a tumor suppressor or oncogene depending on the cellular context (reviewed in (Zhang et al. 2018)). YAP1 is important in regulation of cell apoptosis, but it can have dichotomous roles by promoting either pro- or anti-apoptotic functions. Initial evidence showed that YAP1 acts as a tumor suppressor that binds to P53 family members P63 and P73 via its WW domain and enhances their proapoptotic function (Strano et al. 2001; Strano et al. 2005). In addition, diminished YAP1 expression has been reported in some tumor types and was linked to shorter patient survival (Yuan et al. 2008; Cottini et al. 2014). By contrast, a multitude of studies revealed the pro-oncogenic functions of YAP1, largely attributed to the pro-proliferative and pro-survival transcriptional program elicited by its interaction with the family of TEAD transcription factors (TEAD1–4) (Zhao et al. 2007; Liu-Chittenden et al. 2012). Moreover, elevated and nuclear YAP1 staining and inactivating mutations in upstream Hippo pathway members are frequently found in a variety of cancers (discussed in detail below) (Visser and Yang 2010; Deel et al. 2015; Petrilli and Fernandez-Valle 2016).

YAP1-mediated regulation of proliferation and migration of tumor cells

High YAP activity has been shown to positively affect proliferation, survival, stemness, invasiveness and metastatic behavior, as well as therapy resistance of tumor cells in different cancers (Zanconato et al. 2016; Thompson 2020). The growth and proliferation-promoting functions of YAP1 are exemplified by the organ overgrowth observed in Drosophila upon Yorkie overexpression and/or deletion of Hippo tumor suppressors (Justice et al. 1995; Xu et al. 1995; Tapon et al. 2002; Harvey et al. 2003; Huang et al. 2005). Similarly, expression of hyperactivated S127/397A-YAP1 resulted in increased cell proliferation and growth of cell lines in vitro as well as tumor growth in mice in vivo (Zhao et al. 2010b; Szulzewsky et al. 2020). De-regulation of YAP activity has also been shown to cause excess proliferation in multiple tissues, including liver, gastrointestinal tissues, skin, and heart (Camargo et al. 2007; Dong et al. 2007; Heallen et al. 2011; Schlegelmilch et al. 2011). In addition, YAP1 knockdown reduced the growth and proliferation in vitro and/or the ability to form tumors upon transplantation into mice of several cancer cell lines (Muramatsu et al. 2011; Nallet-Staub et al. 2014; Hiemer et al. 2015; Pei et al. 2015; Zhang et al. 2015; Vigneswaran et al. 2020), whereas overexpression of hyperactivated YAP1 in cancer cells with low endogenous YAP1 expression led to an increase in proliferation (Hiemer et al. 2015; Yu et al. 2018). TEAD-dependent YAP1 functions have also been linked to invasive and metastatic behavior of tumor cells (Lamar et al. 2012) and knockdown of YAP1 expression has also been shown to decrease the migration of several tumor cell lines in vitro and/or the metastatic phenotype in mice in vivo (Chen et al. 2012; Hiemer et al. 2015; Pei et al. 2015; Kim et al. 2017; Choi et al. 2018).

Roles of YAP1 in in cancer therapeutic resistance

YAP activity was linked to therapy resistance in different cancer types. For example, increased YAP activity in esophageal cancer induced EGFR expression and was positively correlated with resistance to 5-fluorouracil and docetaxel, whereas knockdown of YAP1 sensitized cells to these drugs (Song et al. 2015). Furthermore, YAP1 expression correlated with resistance of urothelial cell carcinomas and oral squamous cell carcinomas to cisplatin treatment and knockdown of YAP1 sensitized cells from both cancer types to cisplatin treatment (Yoshikawa et al. 2015; Ciamporcero et al. 2016). YAP1 expression and activity was also linked to resistance to radiation therapy in Glioblastoma and Medulloblastoma, two different types of brain cancer (Fernandez et al. 2012; Alexander et al. 2020). YAP1 expression was shown to confer radio-resistance in Sonic Hedgehog medulloblastoma by promoting ongoing proliferation after radiation (Fernandez et al. 2012). YAP1 enabled the tumor cells to enter mitosis with un-repaired DNA through driving insulin-like growth factor 2 (IGF2) expression and AKT activation. Similarly, YAP activity was also linked to treatment resistance and recurrence in a mouse model of glioblastoma (Alexander et al. 2020). In these tumors YAP1 was expressed in a stem-like and highly radio-resistant cell population that was enriched and proliferating 72 hours post-radiation and contributed to tumor-relapse following radiation therapy. By contrast, another study has shown that inactivation of LATS2 or NF2 or forced expression of hyperactivated YAP1 actually sensitizes several pancreatic cancer cell lines to gemcitabine treatment, indicating that the effect of YAP1 on chemoresistance might be context (in vitro 2D, in vitro 3D, in vivo xenograft or in vivo autochthonous), cell type or cancer type specific (Gujral and Kirschner

2017). This study found that inhibitory Hippo pathway signaling enhanced gemcitabine metabolism and export and Hippo inactivation sensitizes a diverse panel of cell lines and human tumors to gemcitabine in 3D spheroid and mouse xenograft tumors. Taken together, these studies highlight a pro-tumorigenic and also context dependent pro- and anti-therapy resistance functions of YAP1 in a large variety of cancers.

Roles of YAP1 in metabolic reprogramming of cancer cells

Dysregulation of metabolic pathways is observed in a variety of cancers. Cancer cells often display an increased uptake of glucose yet use less glucose for the TCA cycle and oxidative phosphorylation and instead favor the glycolytic pathway even under aerobic conditions (called aerobic glycolysis or Warburg effect). To compensate for these changes and to satisfy the demand for biosynthetic precursors and NADPH while maintaining the functional TCA cycle, cancer cells often rely on elevated rates of glutaminolysis, in which glutamine is metabolized to generate ATP and necessary biosynthetic precursors (Jin et al. 2016). YAP1 has been shown to directly induce the expression of several key enzymes involved in both aerobic glycolysis and glutaminolysis thereby modulating the activity of these pathways (reviewed in (Koo and Guan 2018; Yamaguchi and Taouk 2020)). In addition, the activity of YAP1 can itself be regulated by several of these metabolic cues (discussed further below).

YAP1 directly up-regulates the expression of several genes involved in glycolysis in different cancer types, including *GLUT3, HK1, HK2, PFKFB4, PFKP, GAPDH, PGK1, PGAM1, LDHA, PDHA1, and PDHB* (Cosset et al. 2017; White et al. 2019). Furthermore, a subset of patient-derived glioma cell lines exhibits an addiction to GLUT3. These cells display high levels of *GLUT3* expression that is dependent on YAP1 and are vulnerable to YAP1 inhibition (Cosset et al. 2017).

YAP1 has also been shown to enhance both the uptake and the metabolism of different amino acids, most prominently glutamine. YAP1 up-regulates the expression of several glutamine transporters important for glutamine uptake, such as *SLC1A5*, *SLC7A5*, and *SLC38A1* (Hansen et al. 2015b; Park et al. 2016; Edwards et al. 2017). YAP1 also promotes glutaminolysis by directly enhancing the expression of GLS1 (responsible for the conversion of glutamine to glutamate), as well as GOT1 and PSAT1, two enzymes that convert glutamate to α-ketoglutarate by transamination (Bertero et al. 2016; Yang et al. 2018). Notably, treatment with a transaminase inhibitor was able to inhibit the growth of YAP1-driven breast cancer cells in vitro (Yang et al. 2018). Other studies have also linked YAP1 to an activation of serine metabolism (Wu et al. 2017) and increased leucin uptake (Hansen et al. 2015b).

Roles of YAP1 in tumor cell immune escape

YAP1 has been shown to contribute to the immune escape of tumor cells in various cancers (reviewed in (Pan et al. 2019)). One mechanism by which tumor cells escape immune surveillance is by inhibiting activation of cytotoxic T cells by expressing the immune checkpoint protein PD-L1. Cytotoxic T cells entering the tumor express PD-1, which upon binding to its ligand PD-L1 attenuates T-cell activation and function. YAP1 contributes to the immune escape of tumor cells by directly binding to the enhancer and activating the

expression of the *PD-L1* gene (Miao et al. 2017; Hsu et al. 2018; Janse van Rensburg et al. 2018; Kim et al. 2018).

YAP1 is also important for the function of immune-suppressive FOXP3+ T-regulatory cells (Tregs) (Fan et al. 2017; Ni et al. 2018). YAP1 expression in Tregs results in an increase in activin signaling and TGFβ/SMAD-dependent activation of these cells. Pharmacological inhibition of either YAP1 or the activin receptor enhanced anti-tumor immunity and survival in a mouse model of melanoma (Ni et al. 2018). Similarly, another study found that in hepatocellular carcinoma YAP1 expression in peripheral blood mononuclear cells is positively correlated with the abundance of Tregs in the tumor tissue and negatively correlated with patient survival (Fan et al. 2017). This effect was due to the direct transcriptional up-regulation of *TGFBR2* by YAP1 in these cells.

Lastly, two recent studies have shown that YAP1 expression is up-regulated in activated CD4+ and CD8+ T cells and that YAP1 functions as an immunosuppressive factor and inhibitor of effector differentiation (Lebid et al. 2020; Stampouloglou et al. 2020). Loss of YAP1 expression in T cells results in an improved ability of T cells to infiltrate and repress tumors; however, the exact mechanisms by which YAP1 attenuates activation of these cells is still unknown.

YAP1 structure and transcriptional control of YAP1 target genes by the YAP1-TEAD complex

YAP1 is a transcriptional co-activator that does not contain a DNA binding domain and its function in regulation of transcription relies on the interaction with several other proteins, such as transcription factors (such as TEADs, RUNX2, SMADs) and chromatin remodeling proteins (Varelas 2014) (Figure 1).

The transcriptional programs activated by YAP1 and its strong growth promoting functions largely depend on its binding to TEAD transcription factors (Vassilev et al. 2001; Zhao et al. 2008; Zhang et al. 2009). The interaction between YAP1 and TEAD transcription factors is mediated by the TEAD interaction domain (TID), located in the N-terminal region of YAP1 (Vassilev et al. 2001; Li et al. 2010). Serine 94 of TID forms two hydrogen bonds with E240 and Y406 of TEAD1 and mediates a direct interaction between YAP1 and TEAD1 (Li et al. 2010). Furthermore, the TID region contains two short helices with an extended loop containing a PXXΦP motif important for the interaction with TEADs (Chen et al. 2010). TEADs themselves do not contain an activation domain and are thought to function in gene activation mostly through their interaction with YAP1. ChIP-Seq experiments demonstrated a large co-occupancy of YAP1 and TEAD peaks (Zhao et al. 2008; Galli et al. 2015; Stein et al. 2015). Ablation of YAP1-TEAD interaction by S94A mutation of YAP1 resulted in the inability to induce the gene expression changes elicited by wild type YAP1 (Zhao et al. 2008). Furthermore, expression of S94A-YAP1 in NIH-3T3 cells was unable to recapitulate the growth promoting effects of wild type YAP1 (Zhao et al. 2008). Functionally, TEADs direct YAP1 predominantly to distal enhancers and super-enhancers, where YAP1 then recruits the p300 acetyltransferase to induce H3K27 acetylation (Galli et al. 2015; Stein et al. 2015). The YAP1-TEAD complex has also been shown to interact with AP-1 to activate

the expression of its target genes (Zanconato et al. 2015; Koo et al. 2020). YAP1 stimulates cell proliferation either directly by controlling the expression of genes involved in cell cycle control, or indirectly by inducing the expression of other transcriptional regulators (Nicolay et al. 2011; Mizuno et al. 2012; Kapoor et al. 2014; Zanconato et al. 2015; Totaro et al. 2018). Prominent YAP1-TEAD target genes include *CTGF, CYR61, NPPB, CCND1, AXL, DKK1, ITGB2, WWC1, AMOTL2 and ANKRD1* (Stein et al. 2015; Wang et al. 2018). Importantly, the YAP1-TEAD complex has also been shown to coordinately regulate a network of proproliferative genes together with MYC (Xiao et al. 2013; Croci et al. 2017). YAP1 binds to promoters pre-bound by both TEAD and MYC and MYC-driven cell cycle entry depends on YAP activity.

Located in close proximity to the TID is the YAP1 14-3-3 interaction domain, that is a target of LATS1/2-mediated phosphorylation of YAP1 at S127 and, when phosphorylated, drives interaction with 14-3-3 proteins and cytoplasmic sequestration of YAP1 (Zhao et al. 2007; Zhao et al. 2010b).

Neighboring the 14-3-3-binding domain are WW protein domains (one or two depending on the YAP isoform) that are involved in protein-protein interactions and recognize a PPxY motif in their protein targets. These WW domains are responsible for the interaction of YAP1 with several other proteins, including transcription factors, such as RUNX2 (Yagi et al. 1999), SMADs (Ferrigno et al. 2002), ERBB4 (Komuro et al. 2003; Omerovic et al. 2004; Haskins et al. 2014), p63/p73 (Strano et al. 2001; Strano et al. 2005; Levy et al. 2007; Levy et al. 2008), and PAX3 (Manderfield et al. 2014). The WW domains also mediate the interaction with several chromatin-remodeling proteins. Both YAP1 and Yorkie, the Drosophila orthologue of YAP1, interact with a PPxY motif in Ncoa6, a subunit of the Trithorax-related (Trr) histone H3 lysine 4 (H3K4) methyltransferase complex, which results in increased H3K4 methylation and active transcription (Oh et al. 2014; Qing et al. 2014). In addition, Yorkie was also shown to use WW domains to interact with GAGA factor (GAF), the Brahma complex, and the Mediator complex to induce H3K4 trimethylation and activate transcription of target genes (Oh et al. 2013; Galli et al. 2015). Similarly, human TAZ was shown to interact with BRM, the catalytic subunit of the SWI/SNF chromatin remodeling complex to activate the transcription of TAZ target genes (Skibinski et al. 2014). Again, this interaction was mediated via the WW domains of TAZ and a PPxY motif in BRM. As mentioned earlier, YAP1 has also been shown to recruit p300 to induce H3K27 acetylation (Stein et al. 2015; LeBlanc et al. 2018).

The extended C-terminal region of YAP1 contains an unstructured transactivation domain (TAD) that is rich in serine, threonine and acidic amino acids (Yagi et al. 1999). The exact biochemical mechanisms of how this acidic C-terminal TAD activates gene expression are unknown, however it resembles the acidic activation domain of herpes simplex virus VP16, suggesting that YAP1, like VP16, can directly interact with components of the transcriptional machinery including TFIIB, TBP, TFIIA, and TFIIH (Vassilev et al. 2001). Interestingly, Yorkie, the Drosophila orthologue of YAP1, does not contain the C-terminal TAD, indicating that the exact mechanism of how YAP1 and Yorkie activate transcription differ at least in part (Zhu et al. 2015). In addition, phosphorylation of YAP1 at Y407 located in the TAD by c-ABL, SRC, or YES can influence the function of YAP1 and its

interaction with other proteins, such as β-catenin or p73 (Sudol et al. 1995a; Levy et al. 2008; Rosenbluh et al. 2012). Finally, a PDZ binding motif located at the very C-terminus of YAP1 mediates the interaction with ZO-2 and is necessary for the nuclear localization and activity of YAP1 (Oka and Sudol 2009; Oka et al. 2010).

YAP1 and TAZ exert overlapping but not identical functions

The Hippo Pathway is highly conserved across species and *YAP1*/*Yorkie* and other key Hippo cascade components were already present in unicellular ancestors (Sebe-Pedros et al. 2012). By contrast, the YAP1 paralogue TAZ is evolutionary much younger and is only found in vertebrates (Pappalardo et al. 2015). YAP1 and TAZ are both required for embryonic development and it is thought that their functions are largely overlapping but not redundant. Homozygous deletion of *Yap1* in mice is embryonically lethality as early as E8.5 (Morin-Kensicki et al. 2006), whereas around one-fifth of mice deficient for *Taz* are viable (Makita et al. 2008), although it is not known if this is due to different tissue expression patterns or differences in their actual transcriptional functions. Recent studies have shown that the transcriptional profiles induced by both YAP1 and TAZ in HEK293 cells largely overlap, however knockout of *YAP1* had a bigger influence on cellular physiology (such as proliferation, cell volume, migration) when compared to knockout of *TAZ*, and *YAP1* knockout cells behaved more similar to *YAP1*/*TAZ* double knockout cells (Plouffe et al. 2018). Another study performing ChIP-Seq for both YAP1 and TAZ in breast cancer cells also demonstrated a large overlap in the function of both proteins (Zanconato et al. 2015). Around 7,100 peaks (92% of YAP1 peaks and 73% of TAZ peaks) were shared between both proteins, indicating that their functions are similar, however not identical. It is unknown what causes the differences in the functionalities of YAP1 and TAZ. Both proteins share around 60% similarity, however there are also prominent differences. YAP1's longest isoform contains two WW domains, whereas TAZ only contains one (Hong et al. 2005). In addition, YAP1 contains an SH3-binding motif (necessary for its interaction with YES) and a proline-rich N-terminal region, both of which are absent in TAZ and TAZ was unable to bind the Yes SH3 domain *in vitro* (Kanai et al. 2000). Furthermore, TAZ contains a second, N-terminal phosphodegron that is not present in YAP1, contributing to the fact that TAZ activity is much more dynamically regulated by protein degradation compared to YAP1 (Huang et al. 2012). Finally, while both YAP1 and TAZ predominantly function through binding to TEADs (Zanconato et al. 2015) and residues necessary for the interaction with TEADs are conserved in TAZ, it does not contain YAP1's PXXΦP motif and can form both heterodimers and heterotetramers with TEADs (Chen et al. 2010; Li et al. 2010; Kaan et al. 2017). In conclusion, YAP1 and TAZ exert largely overlapping, however not identical functions and further studies are necessary to explain these differences.

Regulation of YAP1 by the Hippo Signaling Pathway

The activity of YAP1 is regulated and inhibited by the upstream core kinase cascade of the Hippo signaling pathway (Figure 2). Serine/threonine kinases MST1/2 (orthologues of Drosophila Hippo) interact with SAV1 (orthologue of Drosophila Salvador) and phosphorylate MOB1 (ortholog of Drosophila Mats) and serine/threonine kinases LATS1/2 (orthologues of Drosophila Warts), a critical event resulting in the activation of LATS1/2

(Chan et al. 2005; Hergovich et al. 2006; Praskova et al. 2008). In turn, LATS1/2-MOB1 complex inactivates YAP1 by direct phosphorylation at a series of serine residues (S61, S109, S127, S164, S397 (S381 depending on the YAP1 isoform)), with serine 127 and 397 seeming to be the most important residues for the Hippo Pathway-mediated regulation of YAP1 (Huang et al. 2005; Zhao et al. 2007). Phosphorylation of YAP1 ultimately leads to its inactivation by both nuclear exclusion via binding of 14-3-3 proteins at phosphorylated S127 and proteasomal degradation initiated by phosphorylation of S397 (Zhao et al. 2007; Liu et al. 2010a; Zhao et al. 2010b).

While the above-mentioned core participants of the Hippo pathway play very important roles in regulation of YAP1 and TAZ, mammalian Hippo signaling is very complex and several additional proteins are involved. For example, in addition to MST1/2, LATS1/2 can be also directly phosphorylated and activated by serine-threonine kinases of the MAP4K and TAOK families (Praskova et al. 2008; Meng et al. 2015; Zheng et al. 2015; Meng et al. 2016). In addition to LATS1/2, YAP1 can be also phosphorylated and inhibited by the nuclear kinase PRP4K, cell-cycle kinase CDK1 and AKT (Basu et al. 2003; Zhao et al. 2014; Cho et al. 2018).

Significant information has been accumulated regarding the mechanisms responsible for the upstream regulation of Mst1/2-LATS1/2 cascade (for recent review see (Ma et al. 2019)). One of the most unique aspects of the Hippo signaling pathway is its prominent regulation by extracellular mechanical forces acting on cells exerted by the tissue architecture, extracellular matrix, cellular shapes, cell-cell adhesion and liquid shear stress. In tissue culture, the role of cell contacts and confluency (contact inhibition) in activation of the Hippo cascade and inhibition of YAP1 is especially well documented (Zhao et al. 2007). Inhibition of cell-cell adhesion by loss of adherens junction proteins E-cadherin or alpha-catenin results in prominent YAP1 activation (Kim et al. 2011; Schlegelmilch et al. 2011; Silvis et al. 2011; Karaman and Halder 2018). Gigantic cadherin proteins FAT and Dachsous positively regulate Hippo signaling and inhibit Yorkie activity in Drosophila, and, while the exact mechanism is not conserved in mammals, mouse FAT family proteins have been implicated in the regulation of YAP1 (Silva et al. 2006; Willecke et al. 2006; Willecke et al. 2008; Ragni et al. 2017). The tight junctional and apical-basal cell polarity protein complex CRB3-LIN7cC-PATJ-PALS-MPDZ-AMOT is a prominent negative regulator of YAP1/TAZ (Varelas et al. 2010b). In contrast to cell-cell adhesion structures, cell-substratum adhesion and integrins are strong positive regulators of YAP1/TAZ (Dupont et al. 2011; Elbediwy et al. 2016; Wang et al. 2016b). How exactly the mechanical forces and cell adhesion structures regulate YAP1/TAZ is not completely understood. This regulation may be dependent and independent from the canonical MST1/2-LATS1/2 Hippo signaling pathway (Ma et al. 2019; Zheng and Pan 2019). F-actin cytoskeleton and Rho-family GTPases appear to play a critical role in connecting mechanical forces to YAP1 signaling (Dupont et al. 2011; Aragona et al. 2013). Cell polarity proteins Angiomotins (AMOT, AMOTL1, AMOTL2), Merlin (NF2), Expanded (FRMD6), and the Kibra complex play an important role in the regulation of Hippo signaling and YAP1 (Pan 2010). The Merlin/Kibra/Expanded complex physically associates with both MST1/2 and LATS1/2 and recruits the Hippo kinases to the plasma membrane and the apical membrane domain promoting their activation and phosphorylation of YAP1 (Yin et al. 2013). Interestingly, both Merlin and Angiomotins can directly bind to

YAP1 and sequester it from the nucleus (Varelas et al. 2010b; Furukawa et al. 2017). In addition, Angiomotins promote the Hippo signaling pathway by binding to and activation of Merlin (Li et al. 2015). While Angiomotins are not present in the Drosophila genome, in mammals these proteins may play an important role in connecting mechanotransductive F-actin-mediated signaling to YAP1 activity. Angiomotins associate with F-actin through a conserved F-actin-binding domain, which is also used for binding to YAP1. Thus, F-actin sequesters Angiomotins and blocks their interaction and inhibition of YAP1 (Mana-Capelli et al. 2014).

YAP1 activity can be regulated by several different mechanisms

The first mechanism of YAP1 inactivation is mediated by the exclusion of the YAP1 protein from the nucleus. Recent studies have suggested that even at steady-state conditions YAP1 is continuously shuttled between the nucleus and cytoplasm and the switch between a more nuclear or cytoplasmic localization is a dynamic process that is regulated by several factors and processes (reviewed in (Manning et al. 2020)). Phosphorylation of YAP1 by LATS1/2 results in its binding to 14-3-3 proteins, followed by nuclear exclusion and cytoplasmic sequestration (Oh and Irvine 2008; Ren et al. 2010). In addition, a nuclear exclusion sequence (NES) was identified within the sequence encompassed by leucine 308 to leucine 320 of YAP1 that can be bound by exportin-1 (XPO1) (Wang et al. 2016a). Treatment with the XPO1 inhibitor Leptomycin B resulted in a decrease in XPO1-mediated YAP1 nuclear exclusion and a more prominent nuclear localization of YAP1 (Wang et al. 2016a). The upstream Hippo pathway member NF2/Merlin has also been shown to directly interact with YAP1 and facilitate its nuclear exclusion (Furukawa et al. 2017). Furthermore, Kofler and colleagues identified a nuclear localization sequence (NLS) within amino acids 413 and 427 of human YAP1, as well as an NES in its TEAD binding domain (Kofler et al. 2018). Upon binding to TEAD transcription factors the NES is masked, resulting in nuclear retention of YAP1.

The second mechanism leading to YAP1 inactivation is mediated by proteasomal degradation. Phosphorylation of YAP1 at S397 by LATS1/2 primes YAP1 for additional phosphorylation by CK1δ/ε, resulting in the formation of a phosphodegron that primes YAP1 for ubiquitination by the SCFβ-TRCP E3 ubiquitin ligase and subsequent degradation (Zhao et al. 2007; Zhao et al. 2010b; Azzolin et al. 2014). Interestingly, both mechanisms, nuclear exclusion and proteasomal degradation, seem to independently regulate YAP1 activity. Even though S127A mutation of YAP1 results in a more prominent nuclear localization of YAP1, this does not result in the complete de-regulation of YAP activity and expression of S127A-YAP1 is not sufficient to cause tumor formation in many organs (Zhao et al. 2010b; Chen et al. 2015; Szulzewsky et al. 2020). This is likely due to a compensatory regulation by proteasomal degradation, mediated via phosphorylation at S397 (Zhao et al. 2010b; Chen et al. 2015). In turn, inhibition of both nuclear exclusion and proteasomal degradation by combined S127/397A mutation (2SA-YAP1) or mutation of all five phosphorylated by LATS1/2 serine residues (5SA-YAP1) renders YAP1 fully oncogenic (Zhao et al. 2010b; Zhang et al. 2019; Eder et al. 2020; Szulzewsky et al. 2020). These results indicate that the activity of YAP1 is regulated by several compensatory mechanisms

and a single point mutation - such as a K-Ras G12V mutation that results in oncogenic Ras - is insufficient to de-regulate YAP1 and render it oncogenic.

De-regulation of YAP1 activity in cancer

Elevated YAP1 activity and nuclear staining are observed in several human cancer types and this is often correlated with worse prognostic outcome (Zanconato et al. 2016; Dey et al. 2020). Amplifications of genomic regions harboring YAP1 are frequent events in certain cancers, such as head and neck squamous cell carcinomas (~14% of tumors), esophageal squamous cell carcinomas (~15% of tumors), lung squamous carcinomas (~16% of tumors), and cervical squamous cell carcinomas (~17% of tumors) (Lorenzetto et al. 2014; Sanchez-Vega et al. 2018; Dey et al. 2020). However, it is unclear if YAP1 gene locus amplifications are the tumor initiating events and oncogenic drivers in these tumors or if they are mostly passengers that can potentially contribute to tumor aggressiveness but are not the key genetic changes responsible for malignant transformation. Indeed, simple overexpression of wild type YAP1 in mice is insufficient to cause tumor formation (Szulzewsky et al. 2020). Additional inactivation of upstream Hippo tumor suppressors is potentially necessary to initiate transformation. Similarly, activating point mutations in YAP1 are generally rare in human cancer (Wang et al. 2018). This may be potentially attributed to the fact that LATS1/2 phosphorylate YAP1 at several serine residues and a minimum of two co-occurring point mutations (S127A and S397A) are necessary to fully de-regulate YAP1 and render it insensitive to both Hippo-mediated nuclear exclusion and degradation (Zhao et al. 2007; Zhao et al. 2010b; Szulzewsky et al. 2020). Indeed, while clearly an extremely rare event, a hyperactivated YAP mutant containing several co-occurring serine-to-alanine miss-sense mutations - including S127A and S397A - has been observed in cutaneous melanoma (Zhang et al. 2019).

Recent pan-cancer studies by The Cancer Genome Atlas Research (TCGA) Network identified several recurrent alterations in Hippo Pathway members in human cancers, such as amplifications of YAP1 and/or deletions, loss-of-function mutations, or epigenetic silencing of Hippo Pathway tumor suppressor genes *NF2/Merlin*, *FAT1–4*, *TAOK1–3*, *WW45*, and *LATS1/2*. (Sanchez-Vega et al. 2018; Wang et al. 2018). In addition to loss-of-function events directly involving Hippo Pathway tumor suppressors, several studies have shown that other factors can contribute to de-regulation of YAP1 activity in cancers. These involve miRNAs, mutations in non-Hippo up-stream regulators (e.g. G protein-coupled receptors), viral oncoproteins, mechanical stimuli, and gene fusion events involving *YAP1* and *TAZ* (Figure 3). Below, we will briefly discuss and summarize these findings.

Mutations in Hippo pathway tumor suppressor genes in cancer

FAT proteins

FATs are giant Cadherin proteins and upstream activators of NF2/Merlin and the Hippo pathway. *FAT1–4* loss-of-function events are frequently observed in several human cancer types. The TCGA pan-cancer study reported inactivating *FAT1* mutations or gene deletions in head and neck squamous cell carcinoma, lung squamous cell carcinoma, stomach and esophageal cancer, colorectal cancer, uterine corpus endometrial carcinoma, cervical cancer,

and sarcoma tumors (Sanchez-Vega et al. 2018). Interestingly, *FAT1* inactivation in head and neck squamous cell carcinoma was predominantly observed in HPV-negative cases, indicating that HPV-positive tumors might rely on alternative ways of YAP1 activation (discussed in more detail below). In addition, *FAT2–4* genes were also deleted in several colorectal cancers and uterine corpus endometrial carcinoma tumors (Sanchez-Vega et al. 2018). Furthermore, *FAT1* was homozygously deleted in ~80% of primary oral cancer cases and *FAT1* gene expression was down-regulated or lost in oral cancer cell lines due to either homozygous deletion or promoter methylation (Nakaya et al. 2007; Katoh 2012). Loss of heterozygosity of *FAT1* occurred in ~42% of low grade diffuse astrocytoma and ~63% of glioblastoma samples (Chosdol et al. 2009). Lastly, *FAT1* expression was significantly decreased in invasive breast cancer samples compared to ductal carcinoma in situ and *FAT1* knockdown promoted the progression from ductal carcinoma in situ to invasive breast cancer (Katoh 2012; Lee et al. 2012).

NF2

NF2/Merlin is a potent positive regulator of the Hippo pathway, which can also directly bind to YAP1 and sequester it from the nucleus. Deletion or loss-of-function mutation of the *NF2* gene (most commonly frameshift or nonsense mutation) causes Neurofibromatosis Type 2 (NF2), a rare genetic disorder that results in the frequent formation of several central nervous system tumors, such as schwannomas, meningiomas, and spinal ependymomas (Rubio et al. 1994; Ebert et al. 1999; Ahronowitz et al. 2007; Petrilli and Fernandez-Valle 2016; Lee et al. 2019). YAP1 function is necessary for the proliferation, survival, and *in vivo* tumor growth of *NF2* null Schwann cells (Guerrant et al. 2016). In addition, somatic *NF2* mutations have also been found in a large percentage of malignant mesothelioma patients (Sekido et al. 1995; Cheng et al. 1999; Baser et al. 2002; Sanchez-Vega et al. 2018). The prevalence of functional *NF2*/Merlin inactivation in other cancers is still not fully understood. Somatic NF2 mutations have been found in approximately 4.5% of breast and colorectal cancer cases (Sjoblom et al. 2006). Two studies found only a low prevalence of somatic NF2 mutations in human colorectal carcinoma (2 out of 24 samples and 2 out of 44 samples, respectively), whereas another study found *NF2* loss-of-heterozygosity in 20% of sporadic colorectal cancers and it was found to be more frequent in larger and less differentiated tumors (Arakawa et al. 1994; Rustgi et al. 1995; Cacev et al. 2014). In addition to somatic mutations resulting in the expression of a truncated or inactive NF2/Merlin protein, elevated levels of Merlin phosphorylation at serine 518, which causes inactivation of its tumor suppressive function, may present an alternative route of NF2/Merlin loss-of-function, and this was observed in several cancer cell lines, including melanoma and prostate cancer (Horiguchi et al. 2008; Murray et al. 2012).

TAOK proteins

TAOK1–3 are serine/threonine kinases that can directly phosphorylate and activate LATS1/2 independently of MST1/2. The pan-cancer TCGA studies observed loss-of-function events involving TAOK genes predominantly in stomach and esophageal cancer, colorectal cancer, uterine corpus endometrial carcinoma, sarcomas, and breast invasive carcinomas (Sanchez-Vega et al. 2018; Wang et al. 2018).

MST1/2

MST1/2 are serine/threonine kinases that directly phosphorylate and activate LATS1/2. The pan-cancer TCGA studies identified recurrent loss-of-function events of *MST1* (*STK4*) and *MST2* (*STK3*) genes mostly in colorectal cancer and uterine corpus endometrial carcinoma, whereas they were relatively uncommon in other cancers (Sanchez-Vega et al. 2018; Wang et al. 2018). These loss-of-function events were predominantly caused by point-mutations and gene fusions. Decreased expression of *MST1*/*STK4* is furthermore observed in several hematopoietic malignancies, including myelodysplastic syndrome, classic myeloproliferative neoplasm, and acute leukemias (Stoner et al. 2019). These cancers often exhibit heterozygous deletion of chromosome 20 (harboring the *MST1*/*STK4* gene) and *MST1*/*STK4* was one of nine genes that were down-regulated to subhaploinsufficient levels, and this contributed to malignancy via chronic innate immune activation (Stoner et al. 2019).

LATS1/2

LATS1/2 are serine/threonine kinases that directly phosphorylate YAP1 and inhibit its function. The TCGA pan-cancer study reported *LATS1* and/or *LATS2* loss-of-function events in several cancers. Inactivating mutations, copy number loss, or epigenetic silencing of *LATS2* was observed in low-grade gliomas, EBV-positive esophagogastric cancer, and diffuse large B cell lymphoma (Sanchez-Vega et al. 2018). By contrast, loss of *LATS1* function was observed predominantly in uveal melanoma, colorectal cancer, and uterine corpus endometrial carcinoma. Another study found that *LATS1* was mutated in stomach adenocarcinoma (~6% of cases), uterine corpus endometrial carcinoma (~4%), and bladder urothelial carcinoma (~3%), whereas *LATS2* mutations occurred in uterine corpus endometrial carcinoma (~5% of cases), stomach adenocarcinoma (~4%), and lung adenocarcinoma (~4%) (Yu et al. 2015b).

In summary, pan-cancer TCGA studies indicate that inactivating mutations in Hippo pathway members predominantly occur in *LATS* (especially *LATS2*) and *FAT* (especially *FAT1*) genes, whereas mutations in other Hippo pathway core cascade members were more rare. In addition, very little is known about inactivating events in *MAP4K* genes. The relative rarity of inactivating events in *MST1/2* (*STK4/3*) and *TAOK1–3* genes might be explained by a potential functional redundancy between these two families of proteins, that independently regulate LATS1/2 activity. Therefore, loss-of-function of MST proteins might be compensated by MAP4K and TAOK proteins and vice versa, and therefore not sufficient to de-regulate YAP1 activity. Recurrent *NF2*/Merlin loss-of-function events are predominantly found in cancers associated with hereditary *NF2* mutations, such as schwannomas, meningiomas, and spinal ependymomas. In addition, somatic *NF2* loss-of-function mutations are present in a large percentage of malignant mesothelioma patients but are rare in other cancers.

Additional regulators of YAP1 activity in cancer

G protein-coupled receptors

The Hippo Pathway intersects with several other signaling pathways and the activity of different Hippo Pathway proteins is directly regulated by several non-Hippo Pathway

proteins. Genetic or epigenetic changes affecting these important regulators are frequently observed in several cancer types.

G protein-coupled receptors (GPCRs) constitute a large family of cell surface receptors that transmit diverse extracellular signals. Several studies demonstrated that activation of GPCRs coupled with G proteins Gα12/13, Gαq/11, or Gαi/o upregulates YAP1 signaling (reviewed in (Luo and Yu 2019)). These GPCRs include protease-activated receptors (PARs, thrombin signaling) (Mo et al. 2012), LPA receptors (Yu et al. 2012; Cai and Xu 2013), S1P receptors (Yu et al. 2012), and GPER estrogen receptors (Zhou et al. 2015). They were linked to increased YAP1 activation in such cancer types as ovarian, prostate, breast, lung, pancreatic, colon cancer, and melanoma (Luo and Yu 2019). The direct mechanism how GPCRs modulate the Hippo Pathway and YAP1 activation remains unknown, however, it has been demonstrated that GPCRs activate Rho GTPases which in turn modulate the F-actin cytoskeleton, which can then be sensed by the Hippo Pathway and leads to activation of YAP1 (Yu et al. 2015a; Luo and Yu 2019).

Activating mutations and/or overexpression of GPCRs and G-coupled proteins are frequent events in cancer and there is evidence that these mutations contribute to YAP1 activation in the affected tumors (reviewed in (Nieto Gutierrez and McDonald 2018)). This includes overexpression of *PAR1* and *GPER* in breast cancer (Hernandez et al. 2009; Zhou et al. 2015), activating point mutations in *GNAQ* and *GNA11* in uveal melanoma and blue naevi (Van Raamsdonk et al. 2009; Van Raamsdonk et al. 2010; Feng et al. 2014; Yu et al. 2014; Lyubasyuk et al. 2015), and inactivating mutations in *GNAS* in medulloblastoma and basal-cell carcinoma (He et al. 2014; Kool et al. 2014; Iglesias-Bartolome et al. 2015).

Rho GTPases and the mevalonate pathway

The mevalonate signaling pathway is an essential metabolic pathway that utilizes acetyl-CoA to generate sterol and non-sterol isoprenoids necessary for production of thousands of important biomolecules, such as cholesterol, all steroid hormones, dolichol, heme-A, isopentenyl tRNA, and ubiquinone. The mevalonate pathway has been shown to positively affect the activity of Rho GTPases, which in turn promote the nuclear localization and activity of YAP1 (Sorrentino et al. 2014). In turn, inhibition of HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway, resulted in the inhibition of YAP1. Importantly, Sorrentino et al. demonstrated that mutant p53 activates the expression of sterol regulatory element-binding proteins SREBP1 and SREBP2, which in turn positively regulate the expression of the enzymes of the mevalonate pathway (Sorrentino et al. 2014). Breast cancer cells expressing mutant p53 exhibited activation of both mevalonate signaling and YAP1, whereas knockdown of mutant p53 in MDA-MB-231 cells inhibited YAP1 activity.

O-GlcNAcylation

High glucose uptake and aerobic glycolysis are hallmarks of cancer (discussed in detail above). High glucose levels positively correlate with increased global protein O-GlcNAcylation, a post-translational modification consisting of the addition of an N-acetyl-glucosamine residue (GlcNAc) to serine or threonine amino acids. Increased O-GlcNAcylation is observed in many cancer cells and this can activate YAP1 signaling. O-

GlcNAcylation of YAP1 at several residues inhibits its interaction with LATS1 as well as with the SCFβ-TRCP E3 ubiquitin ligase, thereby increasing its stability and activity (Peng et al. 2017; Zhang et al. 2017).

Wnt pathway

Wnt signaling is a signal transduction pathway playing a pivotal role in regulation of development, normal tissue homeostasis and cancer. Beta-catenin, an essential effector of the canonical Wnt signaling can directly interact with the YAP1 protein (Imajo et al. 2012). The exact mechanisms and the significance of the interaction between YAP1/Hippo and Wnt signaling pathways are very complex and even the functional outcome of this interaction (cooperation versus competition) is sometimes opposite and context dependent (Jiang et al. 2020). YAP1 forms a complex with β-catenin and the transcription factor TBX5 and subsequent phosphorylation of YAP1 by YES1 leads to localization of this complex to the promoters of antiapoptotic genes (Rosenbluh et al. 2012). In turn, cytoplasmic YAP1 inhibits Wnt signaling by facilitating both the degradation and sequestration of β-catenin (Varelas et al. 2010a; Imajo et al. 2012; Azzolin et al. 2014) (reviewed in (Hansen et al. 2015a). YAP1 expression is also positively regulated by Wnt signaling and is a direct target gene of β-catenin (Konsavage et al. 2012). In addition, Protein kinase C zeta (PKCζ) has been shown to inhibit the function of both YAP1 and β-catenin through direct interaction (Llado et al. 2015). PKCζ phosphorylates YAP1 at several residues, including S109 and T110, leading to increased degradation of the YAP1 protein. Importantly, functional inactivation of PKCζ has been reported in colorectal cancer via down-regulation and inactivating mutations, clinically implicating PKCζ as a tumor suppressor (Wood et al. 2007; Ma et al. 2013).

Receptor and non-receptor type tyrosine kinases-PI3K-AKT signaling

Constitutive activation of Tyrosine kinase-PI3K-AKT signaling pathway is one of the hallmarks and a major tumor initiating and promoting factor in human cancer (Biscardi et al. 1999; Fruman et al. 2017). Significant literature implicates Hippo and YAP1/TAZ as important downstream targets of this oncogenic pathway. Epidermal growth factor (EGF) signaling activates YAP1 function by inhibiting LATS (reviewed in (Hansen et al. 2015a)). EGF treatment of immortalized mammary cells inhibits LATS function via a PI3K-PDK1 pathway. PDK1 associates with the Hippo Pathway scaffolding protein SAV1, which in turn leads to the dissociation of the Hippo Core kinase complex, the inhibition of LATS and to the dephosphorylation and nuclear translocation of YAP1 (Fan et al. 2013). Similarly, EGF signaling also activates a EGFR-RASMAPK-AJUBA pathway that likewise activates YAP1 through inhibiting LATS (Reddy and Irvine 2013). The non-receptor type tyrosine kinases of the SRC and FAK families are heavily implicated in human cancer and also activate YAP1 via both Hippo dependent and Hippo independent pathways (Rosenbluh et al. 2012; Kim and Gumbiner 2015; Taniguchi et al. 2015; Elbediwy et al. 2016; Li et al. 2016; Si et al. 2017; Lamar et al. 2019). YAP1 is a functionally essential downstream target of PI3K-AKT signaling pathway activated by either expression of oncogenic PIK3CA or deletion of PTEN (Chen et al. 2019; Roy et al. 2019).

ARRDC3

The ARRDC3 tumor suppressor protein is involved in controlling signaling and trafficking of PAR1. It is down-regulated in several cancer types, including invasive breast carcinomas and renal cell carcinoma (Arakaki et al. 2018; Xiao et al. 2018). ARRDC3 inhibits YAP1 and TAZ activity by directly facilitating their degradation (Xiao et al. 2018; Arakaki et al. 2020). Interestingly, Arakaki et al demonstrated that in invasive breast cancer the tumor suppressive functions of ARRDC3 were mostly related to the inhibition of TAZ, whereas YAP1 function was dispensable for the invasive behavior of these tumor cells (Arakaki et al. 2020).

Leukemia inhibitory factor receptor

Leukemia inhibitory factor receptor (LIFR) has been identified as a breast cancer metastasis suppressor and low *LIFR* expression correlates with poor breast cancer prognosis (Chen et al. 2012). *L*oss of *LIFR* expression leads to YAP1 activation and a YAP1-dependent increase of invasive behavior of breast cancer cells. Re-expression of *LIFR* resulted in an increase of p-S127 (inactivated) YAP1 levels, accompanied by an increase in the levels of phosphorylated (activated) MST1/2 and LATS1; however, the direct mechanism of LIFR-mediated activation of Hippo Pathway signaling is unknown.

MicroRNAs

Several miRNAs have been shown to either positively or negatively influence the activity of YAP1 and/or tumor suppressive Hippo Pathway proteins (reviewed in (Li et al. 2017; Han 2019). Several miRNAs such as miR-550a-3–5p, miR-195, miR-874–3p negatively regulate YAP1 (Li et al. 2017; Han 2019). The tumor-suppressive miR-375 directly represses YAP1, TEAD4, and CTGF expression and was down-regulated in several gastric cancer samples (Kang et al. 2018). By contrast, miR-31 and miR-135b are overexpressed in several cancers and have been shown to inhibit the translation of LATS2 (Liu et al. 2010b; Lin et al. 2013; Mitamura et al. 2014). Similarly, miR-624–5p and miR-665 are overexpressed in osteosarcoma and hepatocellular carcinoma, respectively, and enhance YAP1/TAZ activity by inhibiting LATS function via down-regulating PTPRB (Hu et al. 2018b; Luo et al. 2019).

The Hippo signaling pathway and its effector YAP1 have a profound impact on biogenesis on many miRNAs, including important regulators of MYC (Mori et al. 2014). Activated YAP1 binds p72 (DDX17), a regulatory component of the miRNA-processing machinery, and prevents its interaction with the microprocessor resulting in widespread inhibition of miRNA production (Mori et al. 2014). In addition, YAP1 can also upregulate expression of miR-29 and miR-130 that inhibit the biosynthesis of the tumor suppressor PTEN (Tumaneng et al. 2012; Shen et al. 2015). High expression of miR-130 family members has been observed in several cancer types, including bladder cancer and gastric cancer (Duan et al. 2016; Egawa et al. 2016).

Viral oncogenes

Historically, research on the biology of oncogenic viruses (or Oncoviruses) has led to important findings on the biology of cancer and oncogenes. The transforming activity of most of these oncogenic viruses arises from incorporated activated cellular oncogenes, such

as the Rous sarcoma virus that harbors a truncated and constitutively active form of *Src*. By contrast, some viruses are oncogenic because they developed their own viral proteins that are able to disrupt cellular signaling pathways. This includes the Merkel cell polyomavirus (MCV or MCPyV) in Merkel cell carcinoma (Feng et al. 2008) and the human papillomavirus in cervical cancer (Bosch et al. 1995). Viral proteins from both of these viruses can positively affect YAP1 function, either indirectly by inhibiting the function of Hippo tumor suppressor proteins or by directly interacting with YAP1 itself. Abundant YAP1 and TAZ positivity has been observed in cervical carcinoma samples (Buglioni et al. 2016) and, in addition, low expression of MST1 was observed in cervical carcinoma cell lines (Morgan et al. 2020). The HPV E6 and E7 proteins have been shown to up-regulate the expression of miR-18a, which in turn down-regulates the expression of the Hippo tumor suppressor MST1, ultimately leading to increased YAP1 activity (Morgan et al. 2020). Concurrently, miR-18a knockdown increased the expression of MST1 and significantly reducing cervical cancer cell proliferation Similarly, both MCV and SV40 small T (ST) antigens have been shown to enhance YAP1 activity via PAK1-dependent inhibition of NF2 (Nguyen et al. 2014). Expression of ST lead to both an increase of PAK1 protein levels as well as active phospho-T423 PAK1, which in turn lead to phosphorylation and inhibition of NF2. Furthermore, knockdown of YAP1 was sufficient to inhibit the transforming properties of ST (Nguyen et al. 2014). In addition, the murine polyomavirus small t antigen (PyST) has been shown to directly bind and stabilize the YAP1 protein (Hwang et al. 2014). Binding to PyST enhanced YAP1 association with the protein phosphatase PP2A, leading to a decrease of phospho-S397 YAP1 and a subsequent reduction of YAP1 protein degradation. A subsequent study from the same lab later showed that also the murine polyomavirus middle T (MT) antigen binds to the WW domains of both YAP1 and TAZ (Rouleau et al. 2016). YAP1 was necessary for MT-mediated transformation of NIH3T3 cells and binding to MT resulted in a dephosphorylation of S397 and stabilization of the YAP1 protein, as well as a localization of YAP1 at the cell membrane. Taken together, these findings demonstrate that activation of YAP1 is an important factor for the transformation function of various viral oncoproteins.

Mechanotransduction

Contact inhibition is a major factor in regulating tissue architecture and cell growth in vitro. Cells can sense external forces and changes in the surrounding tissues and react to these stimuli by changing the tension and organization of their F-actin cytoskeleton (Halder et al. 2012; Zanconato et al. 2016). The architecture of normal healthy tissues has tumor suppressive functions and altered tissue composition, stiffness, and extracellular matrix (ECM) might contribute to oncogenic signaling in tumors (Lee and Vasioukhin 2008). The activity of YAP1 is subject to regulation by these mechanical stimuli, as exemplified by the nuclear exclusion of the YAP1 protein at high cell confluency conditions or when cells are grown on a soft ECM *in vitro* (Dupont et al. 2011; Aragona et al. 2013). Importantly, while LATS1/2 function was dispensible for the mechanotransduction-mediated controls YAP1 activity and localization, it primarily relied on F-actin architecture and Rho activity (Dupont et al. 2011; Aragona et al. 2013). In line with these findings, it has been shown that increased actin polymerization and extra F-actin, caused by the overexpression of the actin nucleation factor Diaphanous (DiaCA), lead to YAP1/Yorkie-dependent tissue overgrowth *in*

vivo in Drosophila (Sansores-Garcia et al. 2011). In turn, overexpression of actin capping proteins, that inhibit the accumulation of F-actin, lead to an inhibition of YAP1/Yorkie activity in Drosophila (Fernandez et al. 2011). A recent study by Panciera et al. has shown that the transformation of primary cells by activated RTK-Ras signaling requires additional mechanical stimuli that resulted in activated YAP1 signaling (Panciera et al. 2020).

YAP1 gene fusions

Recent cancer genome sequencing studies have identified a series of gene fusions involving the N-terminal regions of YAP1 in different tumor types, including Supratentorial (ST) Ependymoma (YAP1-MAMLD1, YAP1-FAM118B) (Pajtler et al. 2015; Pajtler et al. 2019), Epithelioid Hemangioendothelioma (YAP1-TFE3) (Antonescu et al. 2013), Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (YAP1-SS18) (Hu et al. 2018a), Poroma/Porocarcinoma (YAP1-MAML2, YAP1-NUTM1) (Sekine et al. 2019), NF2-wild type Meningioma (YAP1-MAML2, YAP1-FAM118B, YAP1-PYGO1, YAP1-LMO1) (Schieffer et al. 2020; Sievers et al. 2020), and Sclerosing Epithelioid Fibrosarcoma (YAP1-KMT2A) (Kao et al. 2020; Puls et al. 2020) (Table 1, Figure 4). Several of these YAP1 gene fusions are recurrent and their presence defines a separate tumor subtype, such as ST-EPN-YAP1 ependymoma (YAP1-MAMLD1) (Pajtler et al. 2015) or Epithelioid Hemangioendothelioma (YAP1-TFE3) (Antonescu et al. 2013). In addition, gene fusions involving TAZ have also been recurrently identified in different cancer subtypes, such as WWTR1(TAZ)-CAMTA1 in a subtype of Epithelioid Hemangioendothelioma (Errani et al. 2011; Tanas et al. 2011; Tanas et al. 2016).

These YAP1 gene fusions occur in tumors that generally show a low overall mutational burden (Pajtler et al. 2015; Rosenbaum et al. 2020), suggesting that these fusion transcripts might be the tumor initiating events and oncogenic drivers in these tumors, as well as potential therapeutic targets. We and others (Pajtler et al. 2019; Szulzewsky et al. 2020; Takadera et al. 2020) have recently shown that several of these YAP1 fusion transcripts (YAP1-MAMLD1, YAP1-FAM118B, YAP1-TFE3, and YAP1-SS18) are sufficient to induce tumor formation when expressed either in the brain or in the muscles of prenatal or neonatal mice using somatic cell gene transfer mouse models, strongly supporting the notion that these fusions are the likely oncogenic drivers in their respective tumors.

All examined YAP1 fusion proteins exert TEAD-dependent YAP activity and were able to both activate YAP1-responsive reporter systems and induce the expression of known YAP1 target genes (Pajtler et al. 2019; Sekine et al. 2019; Szulzewsky et al. 2020). The sequence of these YAP1 fusions consists of an N-terminal part of the YAP1 protein fused to the C-terminal part of another protein. Depending on the particular YAP1 gene fusion, different lengths of the N-terminal YAP1 sequence are retained. YAP1-TFE3, YAP1-SS18, and some variants of YAP1-MAML2 only retain the first 107 amino acids of YAP1, that are missing the 14-3-3 binding domain, the WW and the YAP1 transactivation domains (TAD). By contrast, YAP1-MAMLD1 and YAP1-FAM118B retain large parts of YAP1 sequence (up to amino acid 344 and 388, respectively), YAP1-FAM118B retains a part of the YAP1 TAD, although it is unclear if it is still functional. What all N-terminal YAP1 fusions have in common is that they retain the TEAD binding domain (including the S94 residue) but are

truncated upstream of the S397 residue, which is necessary for the Hippo Pathway-mediated proteasomal degradation of YAP1. Most of the known C-terminal fusion partners possess putative transactivation or p300 interaction domains that might surrogate for the YAP1 TAD that is missing in fusions. In fact, truncation experiments have shown that the MAMLD1 TAD is necessary and sufficient for the YAP1-like transcriptional activity of YAP1-MAMLD1 (Szulzewsky et al. 2020).

As stated earlier, the activity of wild type YAP1 is regulated through phosphorylation by LATS1/2, which in turn leads to both nuclear exclusion and proteasomal degradation (Zhao et al. 2007; Zhao et al. 2010b). Phosphorylation of a series of five serine residues is important for this regulation (S61, S109, S127, S164, S397), with S127 (nuclear exclusion) and S397 (proteasomal degradation) being the functionally most important residues (Zhao et al. 2007; Zhao et al. 2010b).

By contrast, the YAP activity of YAP1 fusion proteins is resistant to inhibitory Hippo Pathway signaling (Figure 5). While the YAP activity of wild type YAP1 was significantly reduced upon overexpression of the Hippo proteins LATS1, MOB1, and MST1, the YAP activity of YAP1 fusions was either unaffected (YAP1-MAMLD1, YAP1-FAM118B, YAP1-TFE3) or significantly less affected compared to wild type YAP1 (YAP1-SS18) (Szulzewsky et al. 2020). This is likely mediated by two factors. On the one hand, the YAP1 sequence of all known YAP1 fusion transcripts is truncated upstream of S397 (important for wild-type YAP1 protein degradation) and in vitro experiments at different cell densities indicate that, in contrast to wild type YAP1, YAP1 fusion proteins are not degraded at high cell densities (Szulzewsky et al. 2020). On the other hand, YAP1 fusion proteins displayed a constitutively nuclear localization even at high cell densities and computational mapping and truncation experiments revealed NLS in the different C-terminal fusion partners (such as MAMLD1, FAM118B, TFE3, and SS18) that were responsible for the constitutive nuclear localization of the corresponding YAP1 fusion proteins (Sekine et al. 2019; Szulzewsky et al. 2020). Deletion of this NLS from the YAP1-MAMLD1 sequence led to a purely cytoplasmic localization of the fusion protein and a loss of its ability to induce tumor formation (Pajtler et al. 2019; Szulzewsky et al. 2020). Similarly, WWTR1(TAZ)-CAMTA1 has also been shown to be resistant to inhibitory Hippo Pathway signaling, attributed at least in part to an NLS near the C-terminus of CAMTA1, deletion of which resulted in cytoplasmic localization and a reduced ability to transform NIH3T3 cells in vitro (Tanas et al. 2016).

Moreover, constitutive activation of YAP1 signaling by expression of a two point-mutant (S127/397A-YAP1), that was resistant to both nuclear exclusion and proteasomal degradation, was sufficient to induce tumor formation upon intracranial expression in new born pups, whereas single point-mutants (S127A-YAP1 or S397A-YAP1) were unable to cause cancer (Szulzewsky et al. 2020). In addition, targeted combined knockout of *Lats1* and *Lats2* in Neurod6-positive brain cells resulted in the formation of brain tumors shortly after birth (Eder et al. 2020). These results suggest that YAP1 fusion events represent activating mutations that generated a deregulated YAP1, insensitive to Hippo Pathway-mediated functional inhibition.

RNA-Seq experiments indicated that YAP1-MAMLD1, YAP1-FAM118B, and YAP1-TFE3 shared a core transcriptional signature that overlapped with wild type YAP1. Moreover, Cut&Run experiments demonstrated that all three YAP1 fusions occupied YAP1 target regions. In addition, YAP1-TFE3 also occupied TFE3 target regions, indicating that at least some YAP1 fusion proteins exert activity of both fusion partners. This was further supported by the fact that intracranial tumors caused by expression of YAP1-TFE3 showed a drastically different histomorphology compared to tumors generated by other YAP1 fusions, suggesting that the TFE3 activity contributed to the biology of the tumor cells (Szulzewsky et al. 2020).

Several studies have shown that the YAP activity of several YAP1 fusion proteins (YAP1-MAMLD1, YAP1-FAM118B, YAP1-TFE3, YAP1-SS18), as well as WWTR1(TAZ)-CAMTA1 largely relies on the interaction with TEAD transcription factors (Tanas et al. 2016; Pajtler et al. 2019; Szulzewsky et al. 2020). TEAD binding motifs were enriched in Cut&Run and ChIP-Seq peaks of both human ST-EPN-YAP1 tumors and in vitro-transduced cells expressing YAP1-MAMLD1, YAP1-FAM118B, or YAP1-TFE3 (Pajtler et al. 2019; Szulzewsky et al. 2020) and TEAD1–4 knockdown and/or S94A mutation of the YAP1 fusion sequences both resulted in reduced YAP1 activity (Pajtler et al. 2019; Szulzewsky et al. 2020). Similar results have been observed for WWTR1(TAZ)-CAMTA1 (Tanas et al. 2016).

The ability of YAP1 fusions to form tumors was either completely abolished (YAP1-FAM118B and YAP1-SS18) or significantly reduced (YAP1-MAMLD1 and YAP1-TFE3) by S94A point mutation, which ablates YAP1-TEAD interaction (Szulzewsky et al. 2020). Moreover, treatment with Verteporfin decreased the YAP transcriptional activity of YAP1 fusion proteins as well as inhibited the growth of YAP1-FAM118B-driven mouse tumor cells in vitro (Szulzewsky et al. 2020). These results suggest that inhibition of YAP activity via pharmacological YAP1-TEAD disruption might be a feasible approach for the treatment of tumors displaying activated YAP1 (or TAZ) as well as YAP1 fusion-driven cancers, however further studies will be necessary to address this point.

In summary, all YAP1 gene fusions analyzed to date were oncogenic and functioned by exerting TEAD-dependent YAP activity that was resistant to inhibitory Hippo Pathway signaling, while the activity of the C-terminal fusion partner was able to contribute to the functions of some YAP1 fusions.

Anti-YAP1 therapy

Several small molecule inhibitors against YAP1 function have been reported (reviewed in (Deel et al. 2015)). Some of these inhibitors have been designed to activate the tumor suppressive Hippo Core kinase pathway, e.g. by inhibiting PP2A (Swingle et al. 2009) or by directly activating MST/LATS kinases (Basu et al. 2014). However, these drugs would likely be ineffective in tumors that harbor inactivating mutations in Hippo pathway members, tumors that achieve YAP1 overactivation through Hippo-independent pathways, or YAP1 fusion positive tumors, since YAP1 fusion proteins are resistant to inhibitory Hippo signaling (Szulzewsky et al. 2020). A second class of molecules could attenuate YAP1

function independently of Hippo signaling, by inhibiting the transduction of mechanical stimuli, e.g. by inhibiting the function of RHO/ROCK or destabilizing F-actin (Dupont et al. 2011).

Lastly, the dependence of the YAP1 transforming functions on the interaction with TEAD transcription factors might be an Achilles' heel of this potent oncogene that can be therapeutically exploited. Verteporfin is a small molecule inhibitor that is presently used as a photosensitizer for photodynamic therapy to treat macular degeneration (Verteporfin In Photodynamic Therapy Study 2001), but it has also been shown to inhibit the function of YAP1 by disrupting the interaction between YAP1 and TEADs in a photosensitizer-independent manner (Liu-Chittenden et al. 2012). Treatment with Verteporfin reduced the growth of YAP1-driven tumors in vivo (Brodowska et al. 2014) and recently several other small molecule inhibitors targeting YAP1-TEAD interactions have been developed (Pobbati et al. 2015; Song et al. 2018; Bum-Erdene et al. 2019). The importance of the interaction with TEAD transcription factors is also shared by all analyzed YAP1 fusion proteins and this could make it possible to treat different YAP1 fusion-positive tumors in a similar manner, however, further studies will be necessary to analyze if this could result in regression of established tumors in vivo.

It remains to be seen if anti-YAP1 therapy in general will be sufficient to inhibit the growth of human tumors that display activated YAP signaling. Tumors in which aberrant YAP activity is the underlying tumor-initiating event and the main oncogenic driver, such as YAP1 fusion-driven tumors or potentially also tumors caused by inactivation of Merlin/NF2, are likely to be sensitive to anti-YAP1 therapy. In turn, targeting YAP1 function may or may not be an effective treatment for tumors in which aberrant YAP activity is not a causal event, but rather the result of oncogenic signaling mediated by other oncogenic drivers. These tumors may not exclusively depend on aberrant YAP activity and might use alternative pathways to support their growth. However, recent studies demonstrated that YAP1 contributes to the resistance of melanoma and breast cancer cells to BRAF and HER2 inhibitors, respectively, indicating that anti-YAP1 therapies might be a feasible concomitant treatment to overcome this resistance (Lin et al. 2015; Kim et al. 2016).

Conclusions

In addition to its pivotal roles in normal tissue development, homeostasis, and regeneration, YAP1 also exerts potent pro-oncogenic functions and high nuclear YAP1 staining or elevated expression of YAP1 has been detected in several human cancer types. The mechanisms by which YAP1 activity is de-regulated in human cancers are versatile and differ between cancer (sub)-types, which may have important implications for the efficacy of anti-YAP therapy. In some cancer types de-regulated YAP activity is the actual tumor-initiating event and sustained YAP activity is required for tumor maintenance, such as in tumors harboring YAP1 gene fusions, especially since these tumors generally harbor very few additional mutations; and it is highly plausible that in these tumors anti-YAP therapy might be a feasible strategy. By contrast, in other cancers, such as tumors harboring several co-occurring mutations and/or gains and losses of whole chromosomes, de-regulation of YAP activity may not be a bona fide oncogenic driver but rather a consequence of aberrant

oncogenic signaling. In these tumors YAP activity might rather contribute to aggressiveness and/or resistance to therapy, but inhibition of YAP activity itself might not be sufficient to inhibit the growth of these tumors. Further studies will be necessary to determine if targeting YAP1 in these cancers could be a possible approach in combination with other drugs to overcome treatment resistance.

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Highlights:

- De-regulation of YAP1 activity plays important roles in the progression, aggressiveness, and therapy resistance of several human cancers
- The mechanisms that facilitate the de-regulation of YAP1 activity in human cancers are versatile and include inactivation of tumor suppressive upstream Hippo Pathway regulators (such as LATS, NF2, or FAT), activation by intersecting pathways (such as GPCRs, the Wnt pathway, or the mevalonate pathway), miRNAs, or viral oncogenes
- YAP1 gene fusions are the likely oncogenic drivers in several subtypes of human cancers and constitute a novel type of activating YAP1 mutation, that renders YAP activity resistant to inhibitory signaling from the Hippo pathway
- Therapeutic targeting of YAP activity by inhibiting the YAP1-TEAD interaction might be a feasible approach, but efficacy might depend on whether YAP activity is an actual oncogenic driver and required for the maintenance of a particular tumor

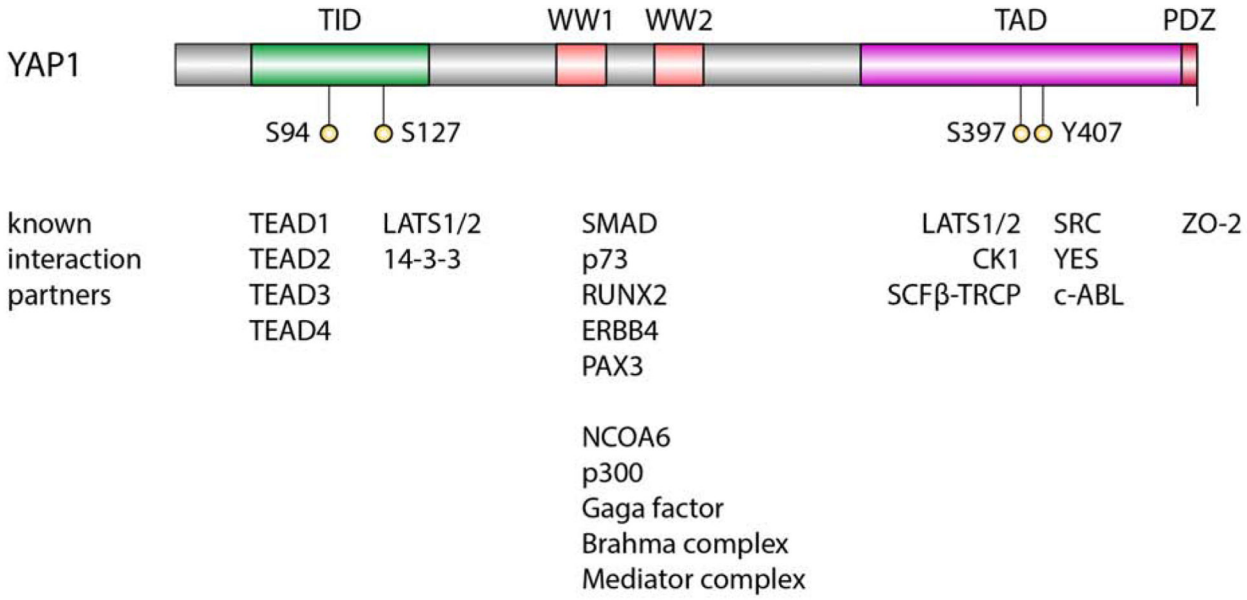


Figure 1 –.
Overview YAP1 protein domains and interaction partners

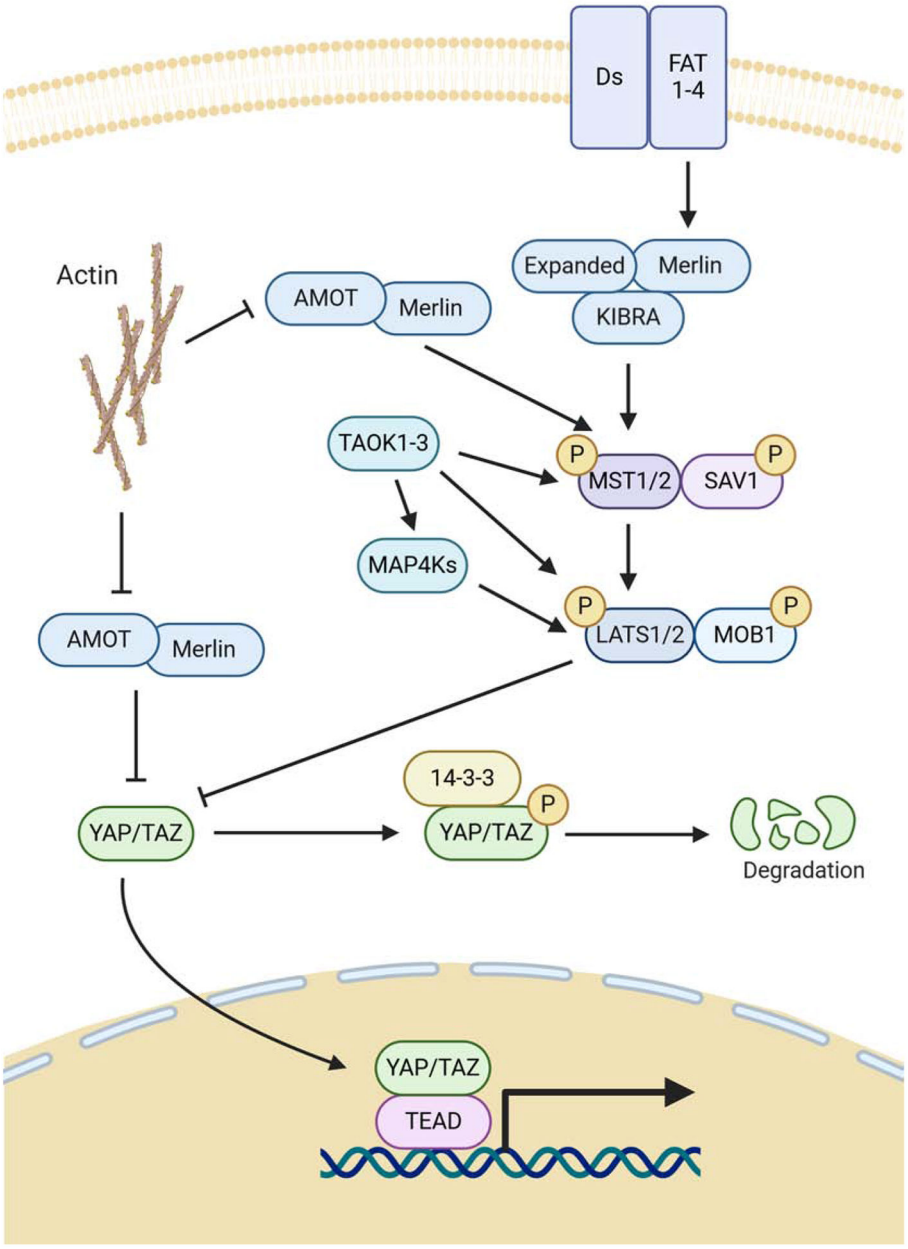


Figure 2 –.

Hippo Core kinases and resulting regulation of YAP1. Figure was created with BioRender.com.

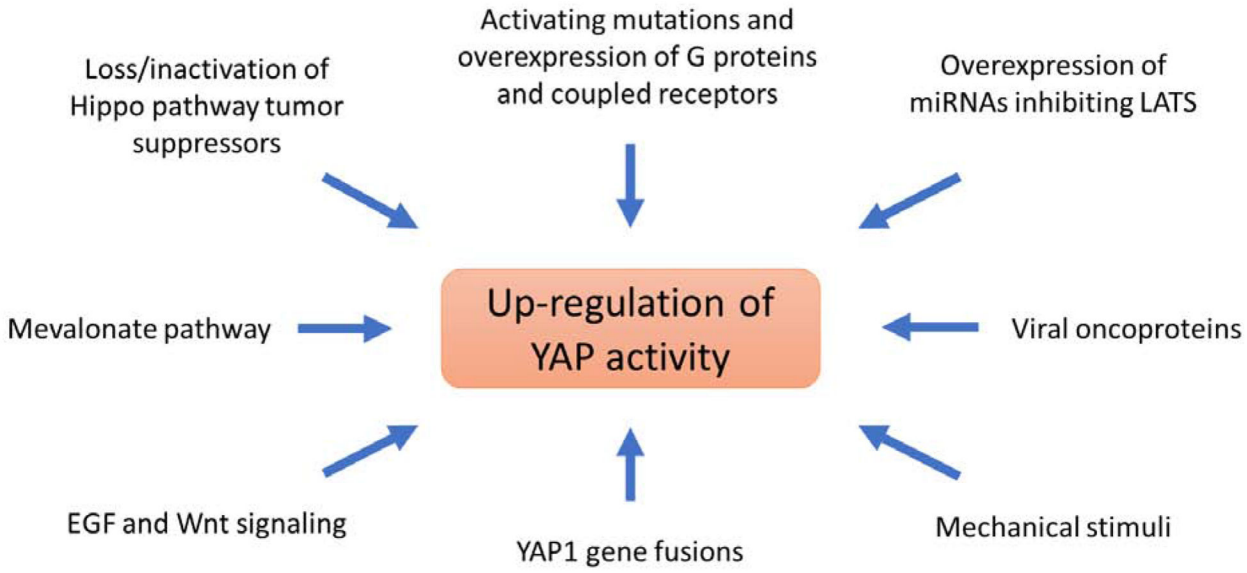
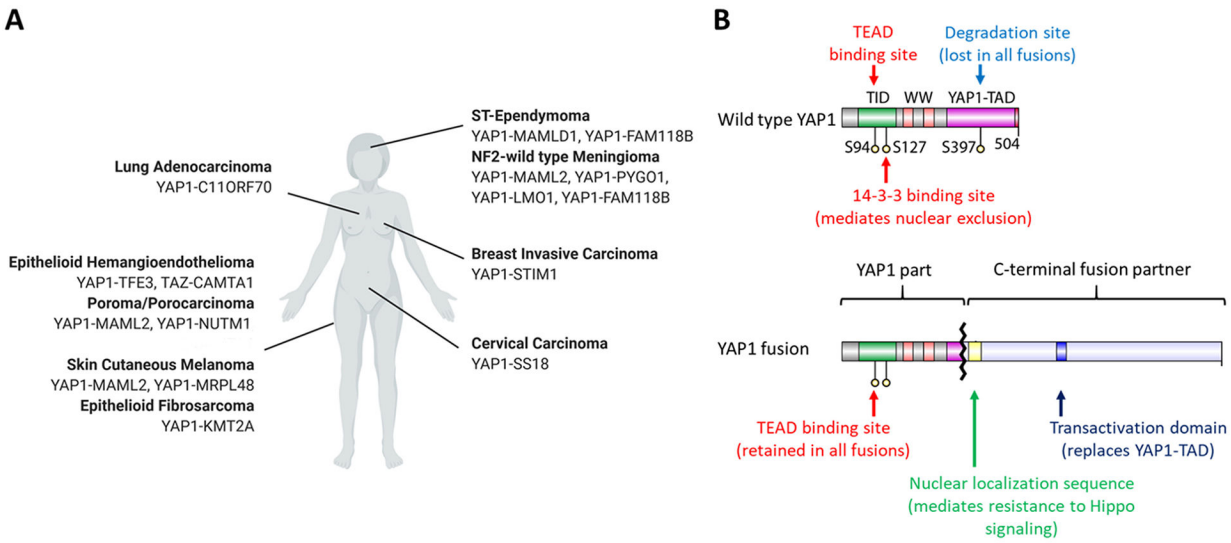


Figure 3 –.
Mechanisms of YAP1 de-regulation in cancer



C Hallmarks of YAP1 fusion proteins

1. Retain the YAP1 TEAD binding site and exert TEAD-dependent YAP activity
2. Transactivation domains of the C-terminal fusion partners surrogate for the truncated YAP1 TAD
3. YAP1 fusions are resistant to inhibitory Hippo pathway signaling due to
   a) constitutive nuclear localization mediated by a nuclear localization sequence located in the C-terminal fusion partner
   b) resistance to proteasomal degradation mediated by the loss of YAP1 S397
4. Some YAP1 fusions show activity of the C-terminal fusion partner that might contribute to their oncogenic functions

Figure 4 –.

YAP1 and TAZ fusions in different cancer types. A: Overview of known YAP1 and TAZ gene fusions and the cancer types they are found in. B: Structural features that are shared between known YAP1 fusion proteins. All known YAP1 fusions retain the YAP1 TID domain necessary for binding to TEADs and lose the S397 residue of wild type YAP1 important for Hippo-mediated proteasomal degradation. In addition, the C-terminal fusion partner contains a nuclear localization sequence that mediates the nuclear localization of the YAP1 fusion proteins. The C-terminal fusion partner also contains a transactivation domain (TAD) that surrogates for the YAP1 TAD that is lost in the YAP1 fusions. C) Hallmarks of known YAP1 fusions. Figure was created with BioRender.com

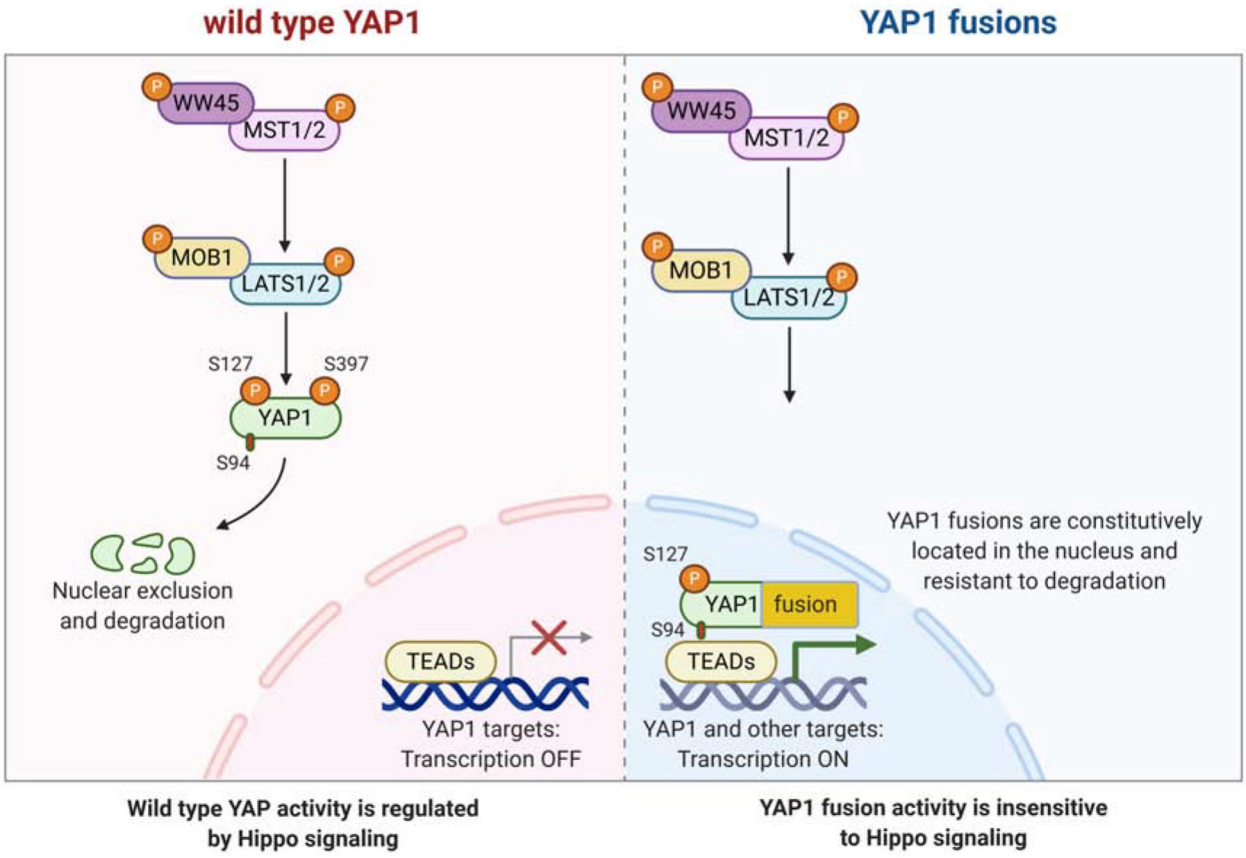


Figure 5 -

Oncogenic mechanisms of YAP1 fusions. Left: Regulation of wild type YAP1 activity by the Hippo pathway. Right: YAP1 fusion proteins are resistant to Hippo pathway-mediated regulation, due to both constitutive nuclear localization (mediated by the nuclear localization sequence present in the C-terminal fusion partner sequence) and resistance to proteasomal degradation (mediated by the loss of YAP1 S397 in the fusion protein). Figure was created with BioRender.com

Table 1:

Summary of recurrent YAP1 and TAZ fusions identified in human cancers.

Fusion	Tumor type	Retained YAP1/TAZ amino acids	Retained C-terminal fusion partner amino acids	References
YAP1-FAM118B	ST-Ependymoma; NF2-wild type Meningioma	aa1-aa388 (exons 1–7)	aa1-aa351 (entire sequence)	(Pajtler et al. 2015; Schieffer et al. 2020)
YAP1-KMT2A	Sclerosing Epithelioid Fibrosarcoma; Fibromyxoid Sarcoma	1) aa1-aa267 (exons 1–4) 2) aa1-aa328 (exons 1–5)	1) aa1112-aa3969 (exons 5–36) 2) aa1053-aa3969 (exons 4–36)	(Kao et al. 2020; Puls et al. 2020)
YAP1-LMO1	NF2-wild type Meningioma	aa1-aa267(exons 1–4)	aa9-aa156 (exons 2–4)	(Sievers et al. 2020)
YAP1-MAMLD1	ST-Ependymoma	1) aa1-aa328 (exons 1–5) 2) aa1-aa344 (exons 1–6)	1) aa58-aa774 (exons 3–7) 2) aa33-aa774 (exons 2–7)	(Pajtler et al. 2015)
YAP1-MAML2	Head and Neck Carcinoma; Nasopharyngeal Carcinomas; NF2-wild type Meningioma; Ovarian Carcinoma; Poroma/Porocarcinoma; Retiform and Composite Hemangioendothelioma	1) aa1-aa107 (exon 1) 2) aa1-aa328 (exons 1–5)	1) aa172-aa1152 (exons 2–5) 2) aa172-aa1152 (exons 2–5)	(Picco et al. 2019; Sekine et al. 2019; Antonescu et al. 2020; Sievers et al. 2020)
YAP1-NUTM1	Poroma/Porocarcinoma	1) aa1-aa229 (exons 1–3) 2) aa1-aa267 (exons 1–4)	1) aa6-aa1132 (exons 2–7) 2) aa6-aa1132 (exons 2–7)	(Sekine et al. 2019)
YAP1-PYGO1	NF2-wild type Meningioma	aa1-aa267(exons 1–4)	aa17-aa419(exons 2–3)	(Sievers et al. 2020)
YAP1-SS18	Cervical Squamous Cell Carcinoma; Endocervical Adenocarcinoma	aa1-aa107 (exon 1)	aa1-aa418 (entire sequence)	(Szulzewsky et al. 2020)
YAP1-TFE3	Epithelioid Hemangioendothelioma	aa1-aa107 (exon 1)	aa179-aa575 (exons 4–10)	(Antonescu et al. 2013)
TAZ-CAMTA1	Epithelioid Hemangioendothelioma	1) exons 1–2 2) exons 1–4	1) exons 9–23 2) exons 8/9–23	(Errani et al. 2011; Tanas et al. 2011)