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YAP1 (Yes-associated Protein 1)

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Gene Symbol: YAP1
Other Names: YAP, YAP65, Yorkie (Yki)

1. General Information

YAP1 (Yes-associated protein; Hugo Nomenclature HGNC:16262), also known as YAP65, is the major downstream mediator of the mammalian Merlin/Hippo pathway. YAP1 was originally identified and named by its ability to associate with the SH3 domain of the tyrosine kinase YES1 (Yamaguchi Sarcoma viral oncogene homologue 1). Within the human genome, YAP1 is located on chromosome 11q13 with partially duplicated pseudogenes YAP1p1, YAP1p2 and YAP1p3 located on chromosomes 6q24, Xp23 and 6q22. Its corresponding orthologous mouse and rat genes are located on chromosomes 9 and 8, respectively. While most major players in the Merlin/Hippo pathway were identified in Drosophila, YAP1 was first identified in mammals; Yorkie (Yke) the Drosophila ortholog of YAP was cloned and functionally characterized approximately 5 years later (16).

YAP1 is expressed throughout development, organogenesis, and postnatal growth and it is functionally important in many types of cells. Therefore, aberrations in YAP1 are involved pathogenesis of multiple organs, including the pancreas.

YAP1 protein structure & its functional implications

YAP1 is a 488 amino acid protein with several structural domains **(Figure 1)**. The two most functionally important structural domains are the TEAD DNA factor interaction domain and either one or two WW domain(s), so named because of two tryptophan residues within a span of four well-conserved aromatic amino acids (7). In addition, there is a Src Homology 3 (SH3) protein-protein interaction binding motif and a transcriptional transactivation (PDZ) domain at the carboxy terminus of this protein. The PDZ domain at the end of the protein has a proline-rich region, where it binds related kinases (31).

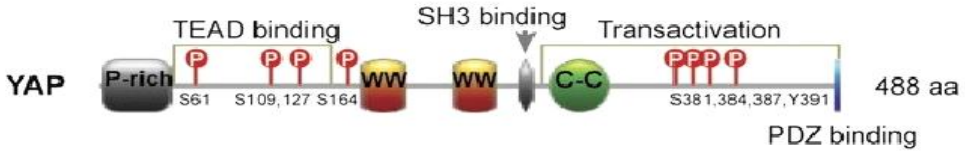

Figure 1. Graphical representation of the structure of YAP1. Reproduced with permission from (46).

YAP signaling and intracellular function

The cannonical YAP1 signaling occurs via the mammalian NF2/Merlin – Mst1/2 – Lats1/2 – YAP/TAZ pathway (12, 46) **(Figure 2)**. The pathway is initially activated via incompletely understood, perhaps by cell-cell contact, paracrine or autocrine signals that affect adherin and cytoskeleton-interacting proteins on cell surface (47). These signals lead to conformational change in the cytoskeletal protein Merlin (Moesin-Ezrin-Radixin-Like Protein, also called Neurofibromin 2 or NF2) and eventually the activation of protein kinase A (PKA) and Ste20-like kinases Mst1 and Mst2 (Mst1/2). Mst1/2 in association with adapter proteins like Salvador-1 activate large tumor suppressor 1 and 2 (Lats1 and 2), which in turn phosphorylate the transcriptional regulator Yes-associated protein 1 (YAP1). Phosphorylated YAP1 is sequestered within the cytoplasm and marked for proteosome-mediated degradation. In its de-phosporylated state, YAP1 interacts with transcriptional regulators like Transcriptional Co-Activator with PDZ domain (TAZ) to initiate a program of gene expression required for cell proliferation, growth and perhaps epithelial-mesenchymal transition. Some of the genes directly influenced by YAP1 include epidermal growth factor receptor (EGFR), Axin and Amphiregullin, among many others.

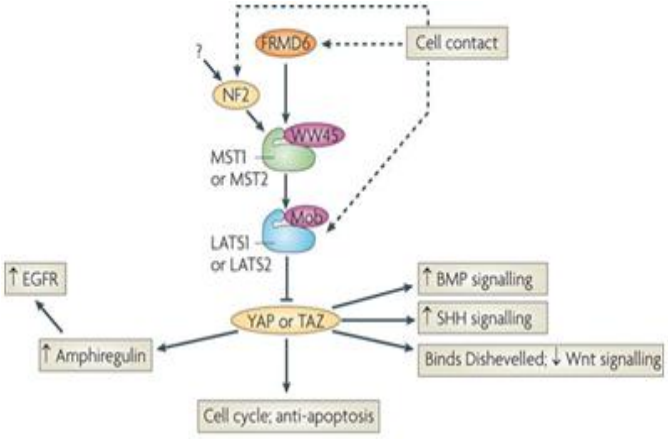

Figure 2. Graphical representation of the canonical Hippo-YAP1 pathway. Reproduced with permission from (27).

The structural complexity of YAP1 and its signaling partners, however, lend it the ability to function as an important hub of signaling networks, integrating crosstalk among multiple other pathways and molecules. Sonic hedgehog (Shh) signaling acts downstream of YAP1 in regulating neuronal differentiation and Gli2 knockdown can rescue the differentiation defect in Yap over-expressing cells (24). In colon cancer and breast cancer cell lines, YAP expression may be driven by aberrant Wnt/beta-catenin signaling (21). In human hepatocellular carcinoma and mouse models of hepatocellular carcinoma, YAP upregulates Jag-1 to activate Notch signaling (35). Metabolic pathway dysregulation, such as increased levels of mevalonic acid, inhibit YAP with activation of Rho GTPases, subsequent YAP phosphorylation and degradation (30, 37).

In normal tissues, YAP regulates the stiffness of many kinds of cells, such as skeletal muscle precursors (4), trabecular meshwork cells (33) and hepatocytes (2). YAP1 is necessary to maintain the phenotype of chondrocytes (48) and pancreatic acinar cells (11). Activated YAP improves cardiac function and promotes cardiac regeneration (8, 38). YAP also plays an important role in overcoming contact inhibition, a fundamental growth control property of normal cells, both in culture and *in vivo*. The loss of a proliferation break at confluence (13) is one of the key characteristics of cancerous cells (47). Furthermore, YAP1 expression is required for the miRNA pre-processing and YAP1 regulates the cell senescence via the cell cycle-regulating kinase CDK6, even without direct binding to its partner(s) (25).

YAP1 has also been extensively studied in regards to its function as an oncogene. Overexpression or aberrant activation of YAP1 promotes neoplastic transformation within hepatocellular carcinoma (25), non-small cell lung carcinoma (36), colon adenocarcinoma (1), melanoma (22), gastric carcinoma (20), ovarian carcinoma (44), skin basal cell carcinoma (28)

and urothelial carcinoma (26), among others. When overexpressed, YAP1 localizes to the nucleus and is present in its active, de-phosphorylated state; this generalization is true of most, but not all of the aforementioned cancers and cancer tissue models. In fact, YAP1 has also been reported to act as a tumor suppressor gene, at least in some breast cancers (23, 40). As such, decreased YAP expression is found to be a bad prognostic marker in luminal A breast cancer (23). Aside from its function within the clonal, aberrantly proliferating population of neoplastic cells, YAP1 was also found to be a necessary part for the mechanotransduction and matrix remodeling with the reactive/desmoplastic cancer stroma (6).

2. YAP in normal pancreatic development and disease

To examine the function of the Merlin/NF2-YAP1 pathway in normal pancreatic growth and development, George et al. generated pancreas-specific Mst1/2 double knockout mice (12), which result in unphosphorylated, constitutively active YAP1. In this setting, they found YAP1 to be detectable mainly in the ductal system and to a lesser extent within the acinar cells, but not in the pancreatic islets. This knockout resulted in a stark phenotype: persistent, transitional structures that maintained a predominantly ductal phenotype but with aspects of acinar differentiation including robust amylase expression. The authors postulated that the observed histopathologic disorganization mimicked acinar-to-ductal metaplasia seen in acinar cell injury and perhaps as early trigger step in neoplasia. They also examined the phosphorylation status of the Hippo/YAP pathway components, showing that phosphorylated YAP was undetectable in the Mst1/2 KO offspring, whereas total YAP1 protein level was found to be elevated. In addition, they confirmed that canonical Merlin/NF2-YAP1 signaling was functional within the exocrine pancreas. In contrast, YAP was not increased in the islets after Mst1/2 knockout. Gao et al (11) also generated double KO mice ($Mst1^{-/-}$ + $Mst2^{fl/fl}$), inducible in the pancreatic anlage via a Pdx1-Cre promoter. They found Mst1 and YAP1, but not MST2, were normally present during the second phase of epithelial-mesenchymal transition (EMT). In contrast, Mst1/2 deletion had no effect on YAP expression, indicating that perinatal YAP repression occurred through a Mst1/2-independent mechanism. Among studies in mouse pancreatic progenitor stem cells, Zhang et al (45) showed an important function of miRNA targeting YAP. MiR-375 could target the 3'UTR of YAP mRNA to decrease its protein and mRNA levels.

Only a few studies specifically address diseases of the exocrine pancreas. Diep et al (9) compared the YAP expression in different pancreatic cell lines and tissues. They found YAP was over-expressed in pancreatic tumor and in cancer cell lines. Knockdown YAP by siRNA and shRNA could diminish the cell viability, proliferation and anchorage-independent growth in cultured cells (9). Zhang et al (45) found YAP was increased in human pancreatic ductal adenocarcinoma (PDAC) and deletion of YAP could halt the progression of early neoplastic lesion to PDAC without affecting the normal pancreatic development. YAP was also shown to be the key effector of KRAS, a critical oncogenic effector within PDAC, and thus constitutes a promising therapeutic target for the majority of pancreatic adenocarcinoma at least in part driven by KRAS (43). Likewise, dysregulation of the Hippo/YAP pathway may also play an important functional role in the pathogenesis of pancreatitis. YAP1 expression is increased in caerulein-induced acute pancreatitis (12). Deletion of upstream components of Hippo pathway (Mst1/2) leads to not only a reduced size of the pancreas and as previously discussed extensive acinar-ductal metaplasia that is phenotypically similar to pancreatitis-like autodigestion. The process is

initiated in development and persists in adult animals, with tissue-wide disorganization and widespread exocrine transitional structures with regions of mixed acinar and ductal phenotype. Whether this comprises a good animal model of pancreatitis or merely a represents a developmental anomaly, remains to be seen. In adult Mst1/2 mutants, the mice phenocopy the histologic changes of acute pancreatitis (AP) as well as mimic gene expression seen in AP, which is at least in part regulated by YAP1 (11).

3. YAP1 and YAP1 signaling pathways as a potential therapeutic targets

As a key component of the Merlin/Hippo pathway, YAP1 has been increasingly recognized as a viable target of drug therapy, particularly in light of its suggested role as a tumor supressor. Pharmacological inhibition of YAP1 and/or its DNA binding partners via blocking of its TEAD domain-mediated interactions leads to reduced target gene expression and blunts YAP1 downstream functions, including proliferation, invasion or phenotypic transdifferentiation like EMT (29). Functional disruption of YAP or more commonly the YAP-TEAD or YAP-TAZ complexes has been explored by several laboratories in many different settings. YAP1 function has been studied in relation to neoadjuvant chemotherapy sensitivization and resistance to therapy. Touil et al reported that YAP1 could be an important target in the task of eradicating dormant cancer cells in colon (34). Huo et al. reported that in hepatocellular carcinoma, over-expression of YAP may cause doxorubicin resistance by increasing phosphorylation of Akt and ERK1/2 (18). Several drugs have been utilized to more or less directly block functional activation of YAP1. Verteporfin (VP) is a cyclic benzo-porphyrin derivative that blocks YAP/TAZ interaction and thereby largely blocks YAP-mediated gene expression. VP is also an FDA-approved drug used to treat macular degeneration and other forms of retinopathy, but more recently it has also been shown to be a promising agent in the treatment of cancer. Yi et al. have shown that VP can inhibit growth of hepatoma cell lines via inhibition of YAP-TEAD complex association and near complete abrobation of YAP1 association with DNA (39). Gurda et al have shown that VP can also inhibit YAP1 and thereby reduce proliferation of cholangiocarcinoma and to a lesser extent non-neoplastic cholangiocytes in a time- and dose-dependent manner (14). Brodowska et al. reported that VP can inhibit the cell growth in a highly aggresive and rapidly fatal retinoblastoma (5). Another drug, Super-TDU VGLL4, is a small peptide that mimics the transactivation domain of a protein Vestigial Like 4 (VGLL4), an endogenous inhibitor of YAP1-TEAD interaction. VGLL4 protein was first identified in Drosophila and shown to function as a transcriptional repressor that inhibits YAP-induced overgrowth and tumorigenesis via its inhibition of YAP1-TEAD complexes (32, 42). Jiao et al. designed a peptide that mimics a segment of VGLL4 and competes with YAP1 for binding to TEAD and other transcriptional partners. They found this peptide to suppress growth of gastric carcinoma both *in vitro* and *in vivo* (19). Another set of studies performed a small chemical screen for pre-existing inhibitors of YAP1 and found that the commonly used sympathomimetic drug Dobutamine can inhibit YAP1 via block of nuclear translocation (3, 10). The promising results of Hippo-YAP1 pathway inhibitors in the laboratory have set the stage for early testing in a clinical setting. Limiting this review to the pancreas: VP has been included in several combination drug trials in the setting of pancreatic adenocarcinoma; recent preliminary report of Stage 1-2 clinical trial of VP as an adjuvant in locally advanced PDAC found it to enhance phototheraphy-induced tumour necrosis and its use to be both feasible and safe (17).

4. Tools to Study YAP1

(a) cDNA clones: YAP1 cDNA has been cloned with a GFP and a Myc tag and is available from OriGene (Rockville, MD). YAP1 peptides or full cDNA clones can also be obtained from Genscript (Piscataway, NJ). Human and mouse siRNA or lentivirus based shRNA which can knock down YAP1 can be purchased from several different commercial companies, including: Sigma, Santa Cruz, Life Technology or empirically designed (successful examples in several articles cited among the references).

(b) Antibodies: Biocompare lists 84 different products by 12 companies. Our primary experience had been with 5 antibodies. We have had a generally positive experience with 2 monoclonal (ab52771 by Abcam and WH0010413M1 by Sigma) and 1 polyclonal antibody from Cell Signal (#4912), but a mixed (Western blot) or negative (immunohistochemistry) experience with a polyclonal antibody (sc-17141,Santa Cruz)**.** A more recently developed monoclonal antibody (#8418, Cell Signal) has been shown to co-detect YAP and TAZ.

(c) Mouse lines/phenotypes: Several strains of mice that harbor genetic modifications of Hippo/YAP1 pathway have been characterized thus far. Conditional YAP knockout or trangenic mice are not commercially available at this point (Fall 2014), but can potentially be obtained from the laboratories that generated them (ie DJ Pan lab at Johns Hopkins). Also, several ES lines are available for purchase (http://mousephenotype.org). By breeding a conditional "floxed" YAP overexpressing transgenic mouse with an inducible and potentially tissue/organ specific CRE 'deleter' mouse, an organ or tissue specific YAP transgenic mice can be developed. Zhang et al, for instance, recently generated YAP conditional knock-out mice and bred them with Albumin-Cre transgenic mouse to obtain a liver specific YAP knock out mouse [42]. Although an exocrine pancreas specific YAP deficient mice have yet to be reported, several exist for the upstream components of the pathway, including Mst1, Mst2 (12), Lkb1 (15) and merlin/NF2 (41). Lastly, a CRISPR system YAP1 mouse KO kit is also available from OriGene.

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