Gene Section

Review

YAP1 (Yes-associated protein 1, 65kDa)

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Identity

Other names: YAP; YAP2; YAP65; YKI
HGNC (Hugo): YAP1
Location: 11q22.1
Local order: Genes flanking YAP1 on 11q22.1 are:
- CNTN5, contactin-5, 11q22.1
- FLJ42335, Hypothetical protein LOC100128386, 11q22.1
- FLJ32810, Rho-type GTPase-activating protein FLJ32810, 11q22.1
- TMEM133, transmembrane protein 133, 11q22.1
- PGR, progesterone receptor, 11q22-q23
- TRPC6, transient receptor potential cation channel, subfamily C, member 6, 11q22.1
- ANGPTL5, angiopoietin-like 5, 11q22.1
- YAP1, Yes-associated protein 1, 11q22.1
- RPS6P17, ribosomal protein S6 pseudogene 17, 11q22.2
- BIRC3, baculoviral IAP repeat-containing protein 3, 11q22.2
- BIRC2, baculoviral IAP repeat-containing protein 2, 11q22.2

Note: YAP interacts with the SH3 domain of c-Yes (and also c-Src), through a stretch of proline residues. YAP protein contains a WW domain that is found in various structural, regulatory and signaling molecules in yeast, nematode, and mammals, and it is involved in protein-protein interaction.

DNA/RNA

Description

The genomic size is 122863 bases and the gene is located on plus strand. YAP1 gene is composed of 7 exons. The open reading frame of the coding region is 1364 bp. No polymorphism of YAP1 is known. SNP: 1590 single nucleotide polymorphisms are present in the human gene according to NCBI database.

Transcription

The human YAP1 coding sequence consists of 1364 bp from the start codon to the stop codon. A differentially spliced isoform of YAP1 (9 exons), with two WW domains known as YAP2 also exists (Sudol et al., 1995).

Pseudogene

No pseudogene of YAP1 is known.
YAP1 (Yes-associated protein 1, 65kDa) Di Agostino S, et al.

Structure of human YAP isoforms. The protein domains and their length (indicated by number of limiting residues) are reported. YAP1 contains a proline-rich domain, a WW domain, a glutamine rich domain and portion of protein that regulates the transcription activation.

### Protein

**Note**

The Yes-associated protein (YAP), a critical mediator of p73 function, binds p73 to regulate its transcriptional activity (Strano et al., 2001) and subsequent cell-death induction (Basu et al., 2003). This binding is negatively regulated by AKT-mediated YAP phosphorylation (Basu et al., 2003) and enhanced by DNA damage (Strano et al., 2005). In addition to increase p73 transcriptional activity via the p300 acetyltransferase (Strano et al., 2005), YAP can stabilize p73 protein in a posttranslational manner by competing with the ITCH E3-ligase for binding to p73 (Levy et al., 2007).

**Description**

**Structure:** YAP protein consists of 454 amino acids, with a molecular weight of 65 kDa. It was identified as a protein that interacted with the non receptor tyrosine kinase c-Yes, which is a member of the Src family (Sudol, 1994). In fact, Yap is able to interact with the SH3 domain of c-Yes (and also c-Src), through a stretch of proline residues; this proline-rich region is able to interact with SH3 domains of many other proteins. In addition Yap contains another binding domain of a different nature. Due to the presence of two tryptophan residues, which appear to be conserved along evolution and that play an important role in the domain structure and function, it was named WW domain (Sudol et al., 1995; Sudol and Hunter, 2000). The WW domain binds to short stretches of prolines (PY motif), and therefore mediating the interaction between proteins. The WW domain of Yap belongs to the first of four different classes that differ in terms of the sequence of the interacting motif, a PPxY in the case of WW type I. Yap has been found to interact with many proteins, whose function often is quite substantially different, and the majority of these interactions are mostly mediated by the WW domain (Bertini et al., 2009).

The interaction with PEBP2 (a RunX transcription factor) was the first example of Yap1 as a co-activator of transcription. The WW domain of Yap1 interacts with the PY motif present in the transcription activation domain of PEBP2 and in this occasion Yap1 was reported for the first time to have a strong intrinsic transactivation activity (Yagi et al., 1999). The transcriptional coactivator Yes-associated protein (YAP) was shown to interact with and to enhance p73-dependent apoptosis in response to DNA damage (Strano et al., 2001; Strano et al., 2005).

<table>
<thead>
<tr>
<th>Interactors of YAP</th>
<th>Reference</th>
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<tbody>
<tr>
<td>YES</td>
<td>Sudol et al., 1995</td>
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<tr>
<td>WBP1 and WBP2</td>
<td>Chen and Sudol, 1995</td>
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<tr>
<td>NFE2</td>
<td>Gavva et al., 1997</td>
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<tr>
<td>RUNX1 and RUNX2</td>
<td>Yagi et al., 1999</td>
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<tr>
<td>EBP50</td>
<td>Mohler et al., 1999</td>
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<tr>
<td>TP53BP2</td>
<td>Espanel and Sudol, 2001</td>
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<tr>
<td>TP73</td>
<td>Strano et al., 2001</td>
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<tr>
<td>TEAD1, 2, 3, 4</td>
<td>Vassilev et al., 2001</td>
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<tr>
<td>SMAD7</td>
<td>Ferrigno et al., 2002</td>
</tr>
<tr>
<td>AKT</td>
<td>Basu et al., 2003</td>
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<tr>
<td>ERBB4</td>
<td>Komuro et al., 2003</td>
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<tr>
<td>HNRNPU</td>
<td>Howell et al., 2004</td>
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<td>LATS1</td>
<td>Hao et al., 2008</td>
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<td>ABL1</td>
<td>Levy et al., 2008</td>
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<td>PML</td>
<td>Lapi et al., 2008</td>
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<td>EGR1</td>
<td>Zagurovskaya et al., 2009</td>
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**Expression**

By Northern blot analysis YAP1 expression shows a major transcript of approximately 5 kb in several human tissues. High expression was found in placenta, prostate, testis, ovary, and small intestine, and lower expression was found in brain, liver, and spleen. No expression was found in peripheral blood leukocytes (Sudol et al., 1995). YAP1 is the predominant isoform and is ubiquitously expressed in the major part of tissues for twelve normal human tissues (out of 28 tissues shown) hybridized against Affymetrix GeneChips HG-U95A-E (GeneNote data) and for 22 normal human tissues hybridized against HG-U133A (GNF Symatlas data) (Su et al., 2004).

**Localisation**

Posttranslational modification of YAP determines its binding and localisation. Lapi et al. (2008) have shown Akt-mediated phosphorylation promotes YAP cytoplasmic retention, demonstrating that active Akt counters cisplatin-induced increases in PML transcription via the YAP-p73 complex. Recently, Levy et al. (2008) have also shown that cisplatin induces ABL1-mediated YAP phosphorylation, resulting in
YAP nuclear localization and increased p73 binding and activation of pro-apoptotic genes.  

YAP binding of p73 and its coordination of other binding proteins probably depend on an integration of phosphorylation by AKT, ABL1, and other kinases. However, the shuttling of Yap between nucleus and cytoplasm has emerged as an important means for regulating the activity of this protein.

**Function**

Yap is a small protein that binds to many transcription factors and modulates their activity. Yap increases the ability of p73 to induce apoptosis as a consequence of damage to the DNA, and therefore its activity was thought to favor tumor suppression. However, other studies have recently shown a role for Yap in cell differentiation, cell transformation and in the regulation of organ size. It has been demonstrated that the Drosophila Hippo pathway has a mammalian equivalent, and that Yap is part of this pathway, where it could stimulate proliferation (Pan, 2007; Harvey et al., 2007).

**Apoptosis:** The transcriptional coactivator Yes-associated protein (YAP) has demonstrated to interact with and to enhance p73-dependent apoptosis in response to DNA damage (Strano et al., 2001; Strano et al., 2005). It has been reported that YAP is phosphorylated by AKT, and such modification impairs YAP-nuclear translocation and attenuates p73-mediated apoptosis (Basu et al., 2003). Recently, it was demonstrated that p73 is required for the nuclear translocation of endogenous YAP in cells exposed to cisplatin and that YAP is recruited by PML into nuclear bodies to promote p73 transcriptional activity (Strano et al., 2005). It was found that YAP contributes to p73 stabilization in response to DNA damage and promotes p73-dependent apoptosis through the specific and selective coactivation of apoptotic p73 target genes and potentiation of p300-mediated acetylation of p73 (Strano et al., 2005). Then, it was described the existence of a proapoptotic autoregulatory feedback loop between p73, YAP, and the promyelocytic leukemia (PML) tumor suppressor gene (Lapi et al., 2008). PML is a direct transcriptional target of p73/YAP. PML contributes to the p73-dependent apoptotic response by regulating YAP stability. Importantly, PML and YAP physically interact through their PVPVY and WW domains, respectively, causing YAP stabilization upon cisplatin treatment, which occurs through PML mediated sumoylation (Lapi et al., 2008).

Together with this proapoptotic role, YAP recently was identified as a tumor suppressor in breast cancer (Yuan et al., 2008). The findings that YAP plays opposing roles in tissue growth/development and DNA damage/apoptosis appear at first contradictory, but this can be explained if YAP binds and activates or inactivates different transcription factors to differentially regulate either pro-growth or pro-apoptotic genes.

**Organ size and cell differentiation:** Yap plays an important role in controlling organ growth. The works done on Drosophila show how a disrupted Hippo signalling pathway has a negative impact on the growth of imaginal discs (Pan et al., 2007) and how the presence of mutated forms of Yap in particular has an effect on size and shape of fly wings (Zhao et al., 2007).

In addition Dong et al. (2007) reported that overexpression of Yap in mice increases liver size, and in the long term it induces nodules which present characteristics of HCC (Dong et al., 2007). This is in accordance with another important study where increased levels of Yap are shown to enlarge liver size in a reversible manner (Camargo et al., 2007).

However, many questions are unsolved. For instance, it would be interesting to check whether the Hippo pathway plays a role in choices taken by Yap during cell differentiation; to verify whether activity of Yap could be extended to a cellular context beside intestine epithelium; to find the molecular mechanism used by Yap to control transcription of those genes that are in charge of cell differentiation; and obviously, a screen for these genes.

**Homology**

**Orthologs:** YAP1 is evolutionarily principally conserved in 8 eukaryotes: Canis familiaris, Pan troglodytes, Bos taurus, Mus musculus, Galus gallus, Danio rerio, Xenopus laevis, Silurana tropicalis. Orthologies between human and Drosophila melanogaster, Caenorabditis elegans and Saccharomyces cerevisiae are quite low. For details see: HomoloGene.

**Mutations**

*Note*  
No mutations of YAP1 are known.

**Implicated in**

**Various cancers**

*Note*  
Overholtzer and collaborators identified a mouse mammary tumor with a small amplicon involving the Yap1 gene. They noted that amplification of the syntenic locus on human chromosome 11q22 is present in different cancers (breast, colon, prostate). Overexpression of human YAP1 in nontransformed mammary epithelial cells induced epithelial-to-mesenchymal transition, suppression of apoptosis, growth factor-independent proliferation, and anchorage-independent growth in soft agar (Overholtzer et al., 2006). They concluded that YAP1 contributes to malignant transformation in cancers harboring the 11q22 amplicon.
Tumor suppression

Note
As previously described, the regulation of p73 activity by YAP has been investigated in the context of DNA-damage signaling. As an activating cofactor for a proapoptotic transcription factor, it was assumed that YAP plays a tumor suppressor role in cancer. YAP has also been identified as an oncogenic progrowth, cell size regulator in both Drosophila melanogaster and mammalian cells (Dong et al., 2007; Zhao et al., 2007).

The mechanism for the growth control role of YAP or its fly homolog, Yki, is the result of its inactivation by the MST2 (HIPPO in fly) pathway, where the tumor suppressor LAT51 kinase (WTS in fly) directly phosphorylates YAP (Yki), inhibiting its coactivation of the TEAD (Scalloped in fly) transcription factor to upregulate pro-growth genes (Zhao et al., 2008).

The MST2/LAT51 pathway can also enhance YAP-p73 binding and activation of proapoptotic genes downstream of Fas signaling in breast cancer cells (Matallanas et al., 2007).

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