



Key signal molecules-----YAP in Hippo Pathway

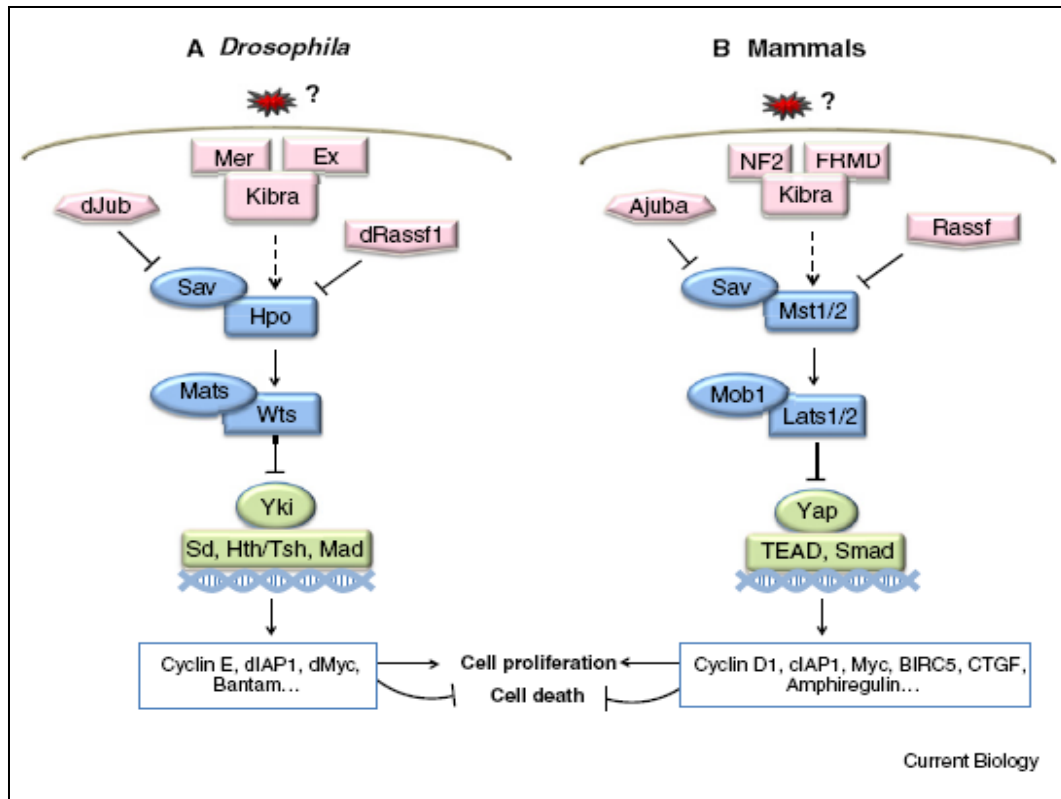
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2013.01.18**

Content

- Background
- General annotation of YAP
- Sequence annotation of YAP
- Phylogenetic analysis of YAP
- Functional analysis of YAP
- Perspectives

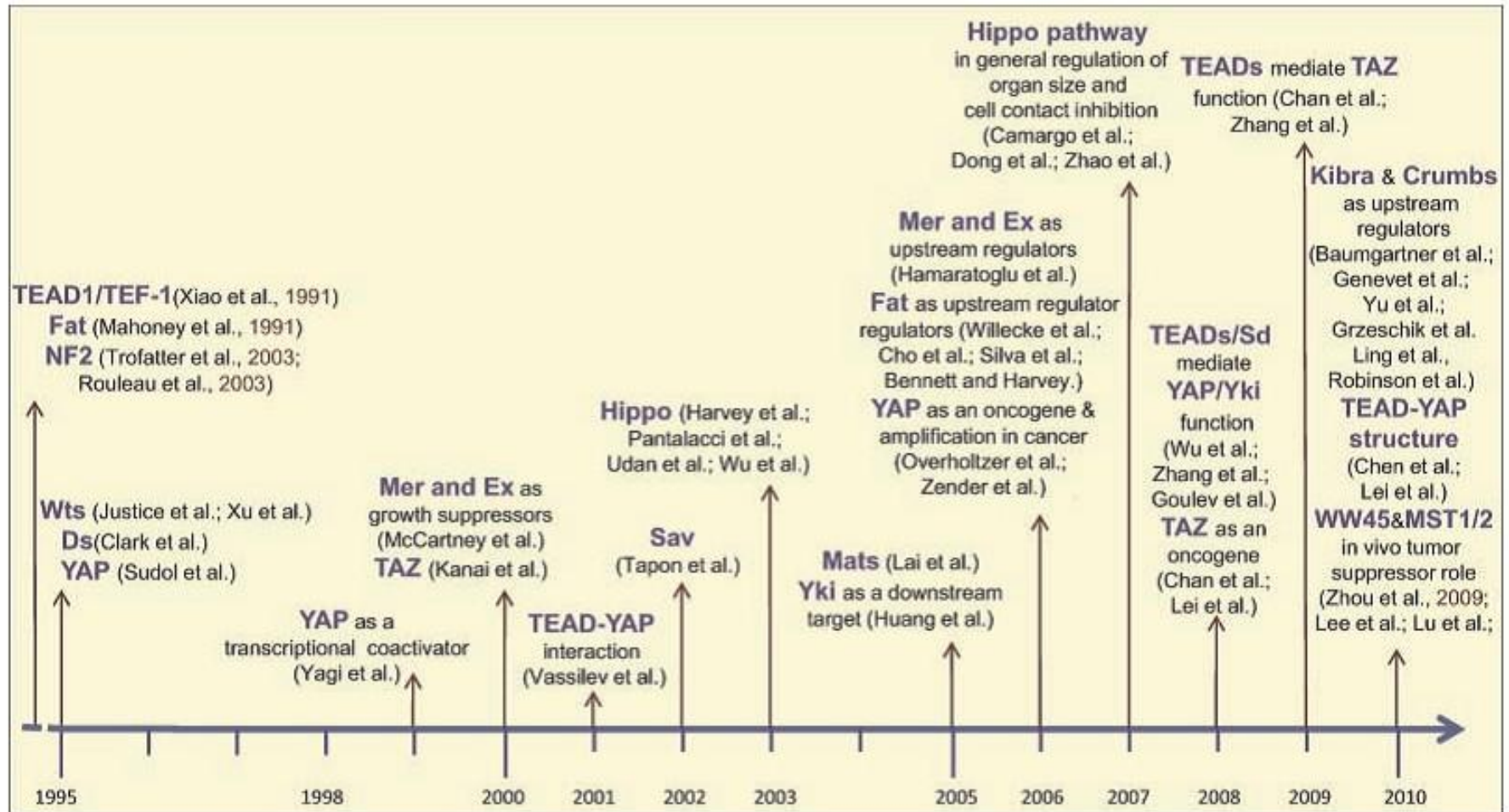
What is Hippo pathway

- Hippo signaling pathway, also known as the Salvador/Warts/Hippo (SWH) pathway
- Controls organ size in animals through the regulation of cell proliferation and apoptosis.



Background

The history of Hippo pathway

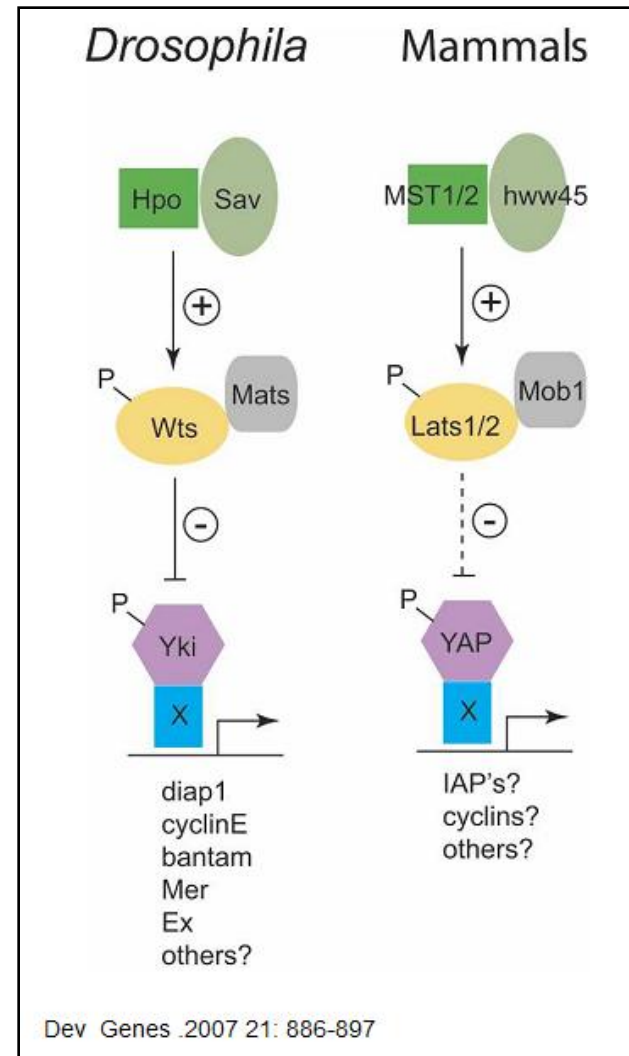


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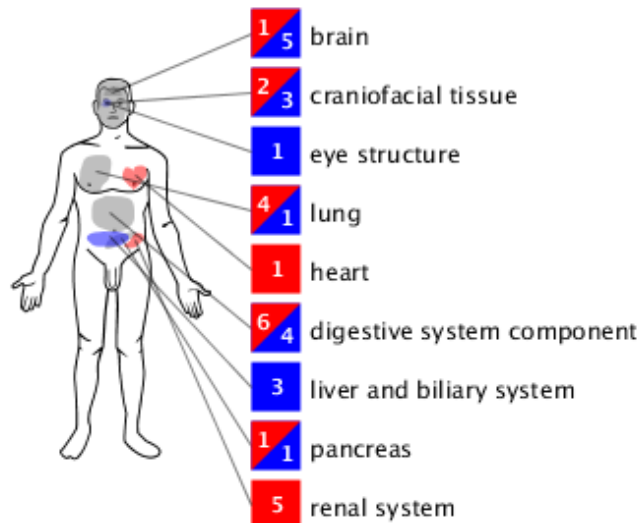
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YAP-----Yes associated protein(Homolog of Yki in Mammals)

- 504 AA, ~65kDa
- 3 isoforms produced by alternative splicing
- A coactivator and a corepressor
- Critical downstream regulatory target in the Hippo signaling pathway



Tissue specificity & Expression Pattern

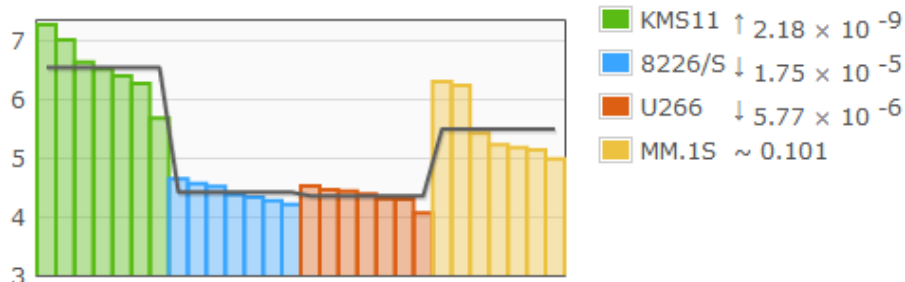


Increased expression seen in some liver and prostate **cancers**

E-GEOD-14519: Transcription profiling of human U266, MM.1s, KMS11, 8226/S multiple myeloma cell lines treated with arsenic [PubMed 19417148](#)

Experimental Factors

cell line Compound treatment time



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Sequence annotation of YAP

Domains

Domain	171 – 204	34	WW 1	
Domain	230 – 263	34	WW 2	
Region	291 – 504	214	Transactivation domain	
Compositional bias	3 – 49	47	Pro-rich	

转录活化结构模型:

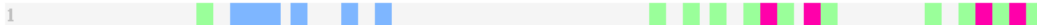
- 1)酸性 α -螺旋结构域含有带负电荷的 α -螺旋区
- 2)富含谷氨酸胶结构域存在于多种转录因子中
- 3)富含脯氨酸结构域常与DNA结合结构域相连

富含脯氨酸结构域(proline-rich domain)是在CTF NF-1中发现的与包括Sp1锌指结构在内的各种DNA结合域相连,即可促进转录。

Target Region 163-209
Protein Length 504
Template PDB Code [2e45A](#)
Template Region 7-50
Sequence Identity 45.00%
E-Value 0.099



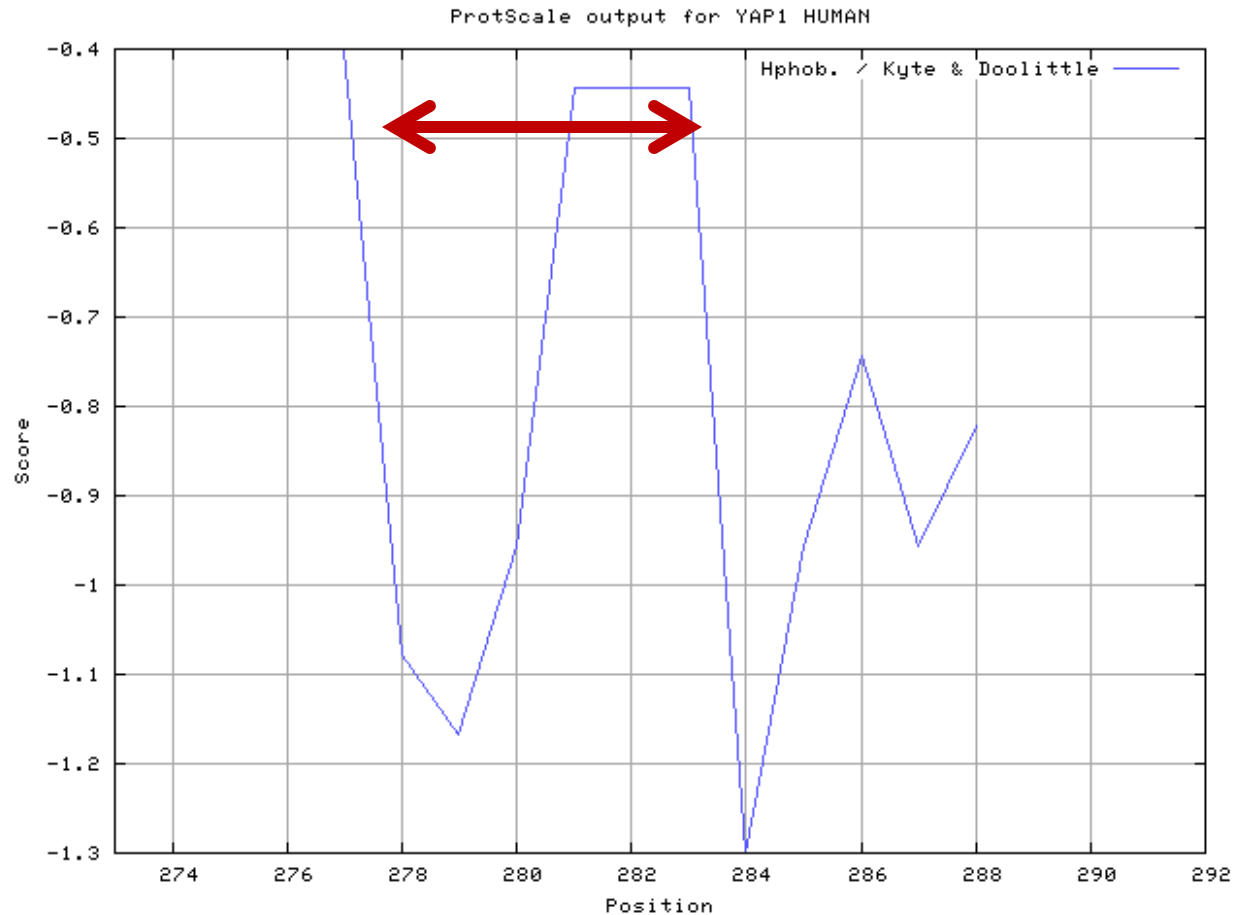
Secondary structure



■ Helix ■ Strand ■ Turn

504

YAP1 hydrophobic analysis

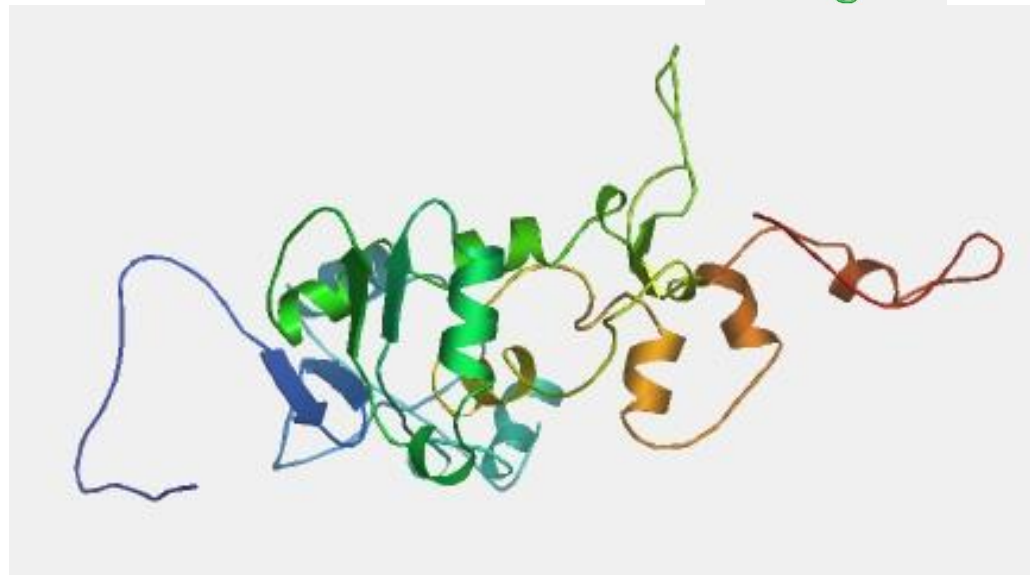
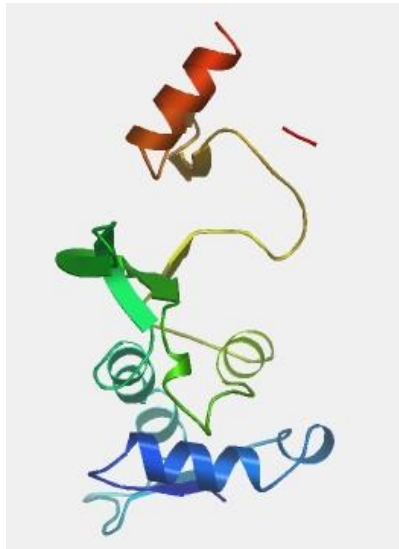
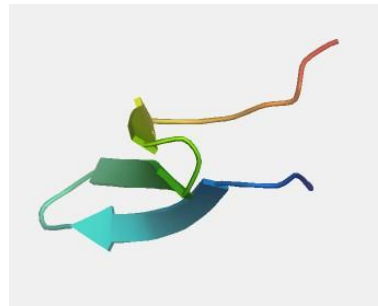
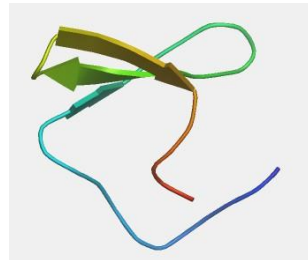
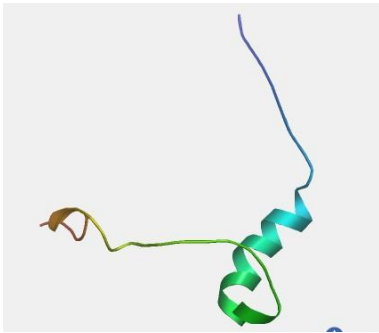


PVKQPPPLAP(278-287)



SWISS-MODEL Workspace

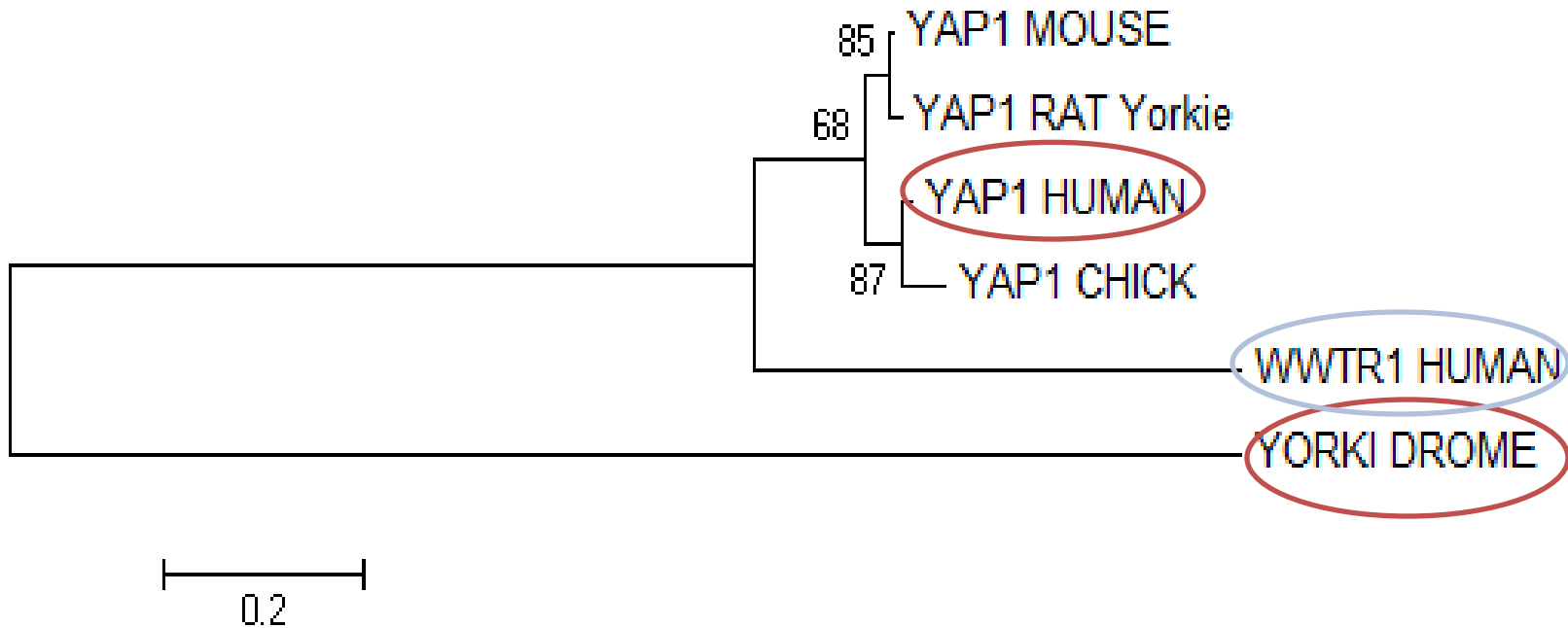
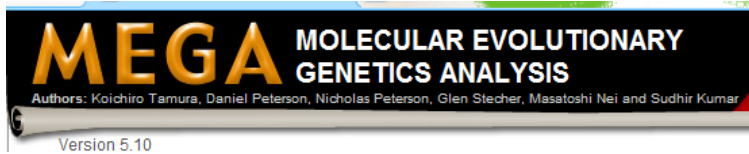
Modelling Tools



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Phylogenetic analysis of YAP



Constructing Method: Maximum Likelihood/ Bootstrap method

Pairwise Alignment Result

LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
654	379.5	111/654 (17.0%)	165/654 (25.2%)	386/654 (59.0%)

1	-----MDPGQQPPPPQAPQGGQPPSQPPQGGPPSPG	33	P46937	YAP1_HUMAN
1	MCACLIAKIILCSFRLYTISAFYMLTTMSASSNTNSLI-----	38	Q45VV3	YORKI_DROME
	* . . . :			
34	GQPAPAATQAAPQAPPAGHQIVHVRGDSETDLEALFNAMNPKTANVPQTVPMRLRKLPD	93	P46937	YAP1_HUMAN
39	--EKEIDDEDMLSPIKSNLNVVRVNDQTDNDNLQALFDSVLPNGDAKRPLQLPLMRKLPN	96	Q45VV3	YORKI_DROME
	: . : . : * : * . * : : * : * * : : * : * * * : * : * * : * : * : * * * :			
94	SFFKPPEPKSHSRQAST---DAGTAGA-----	117	P46937	YAP1_HUMAN
97	SFFTTPAPSHSRANSADSTYDAGSQSSINIGNKASIVQQPDGQSPIAAIPQLQIQSPSQH	156	Q45VV3	YORKI_DROME
	* * . * * . : : : * * : . :			
118	--LTPQHVRHSSPASLQLGAVSPGT-----LTPTGV-----VSGPA	152	P46937	YAP1_HUMAN
157	SRLAIHHSRARSSPASLQQNYNVRARSDAANAANNPNANPSSQQQAPAGTFFPNSAQEFPS	216	Q45VV3	YORKI_DROME
	* : * * * : * * * * * * * . * * * * . * :			
153	ATP-----TAQHLRQSSFEIP-----DDVPLPAGWEMAKTS	183	P46937	YAP1_HUMAN
217	GAPASSAIDLAMNTCMSQDIPMSMQTVHKKQRSYDVVISPIQLNRQLGALPPGWEQAKTN	276	Q45VV3	YORKI_DROME
	. : * : * * * : * : * * * : * : * * * * * : * * * * * * * .			
184	SGQRYFLNHIDQTTTWQDPRKAMLSQMNVITAP-----TSPVQNNMNSASGPLP	233	P46937	YAP1_HUMAN
277	DGQIYYLNHTTKSTQWEDPRIQYRQQQILMAERIKQNDVLTQTTKQTTTSTIANNLGPLP	336	Q45VV3	YORKI_DROME
	. * * * * * * * : * * : * * * * * . * : : * : . . : . * * * *			
234	DGWEQAMTQDGEIYYINHKNTTSWLDPRLDPRFAMNQRISQSAPVKQPPPLAPQSPQGG	293	P46937	YAP1_HUMAN
337	DGWEQAVTESGDLYFINHIDRTTSWNDPRMQSGLSVLDCPDNLVSS-----	382	Q45VV3	YORKI_DROME
	* * * * * : * . * : * : * * * * : * * * * * : : : : . : .			
294	VMGGSNSNQQQMRLQQLMQEKERLRLKQELLRQAMRNINPSTANSFKCQELALRSQLP	353	P46937	YAP1_HUMAN
383	-----LQIEDNL----CSNLFNDAQAIVNPPSSHKPDLEWYKIN---	418	Q45VV3	YORKI_DROME
	* * : * . : . : * : * * : * * : * * : * : * . * .			
354	TLEQDGGTQNPVSSPGMSQELRTMTTNSSDPFLNSGTYHSRDESTDSGLSMSSYSVPRTP	413	P46937	YAP1_HUMAN
419	-----	418	Q45VV3	YORKI_DROME

Two WW domains



Transactivation domain in YAP



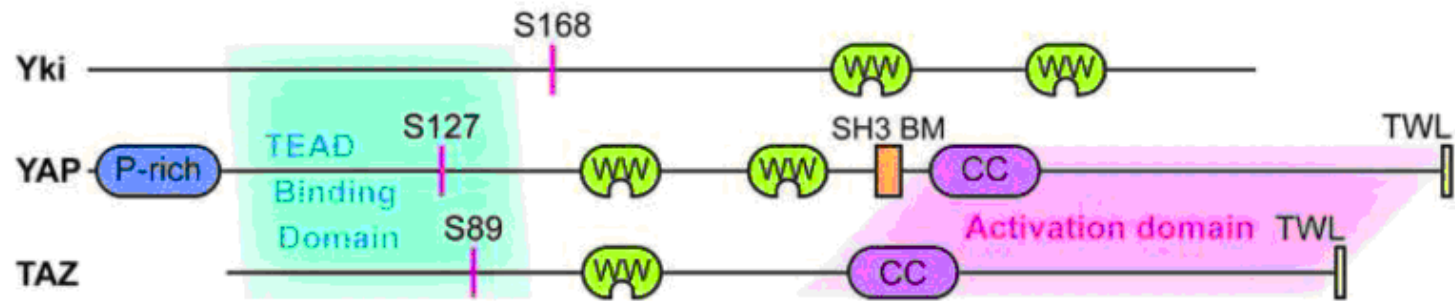


Figure 2. A schematic view of YAP, TAZ, and Yki

YAP is a 65KDa protein with several distinct domains or motifs. It has a proline-rich (P-rich) region at the N-terminal, two tandem WW domains in the middle followed by a Src homology domain 3 binding motif (SH3 BM) PVKQPPPLAP, a coiled-coil domain (CC), and a C-terminal capped by TWL sequence, a PDZ domain ligand. The N-terminal (aa 47-154 in human YAP2, shaded in blue) of YAP was mapped to be the TEAD family transcription factors interaction domain [54], and the C-terminal of YAP (aa 292-488, shaded in pink) rich in serine, threonine, and acidic residues was shown to be a strong transcription activator [51]. The Lats phosphorylation and 14-3-3 binding critical S127 in human YAP2 and its equivalent in Yki and TAZ are also shown. The topology of Yki and TAZ are shown in similar fashion and the proteins are drawn in scale.

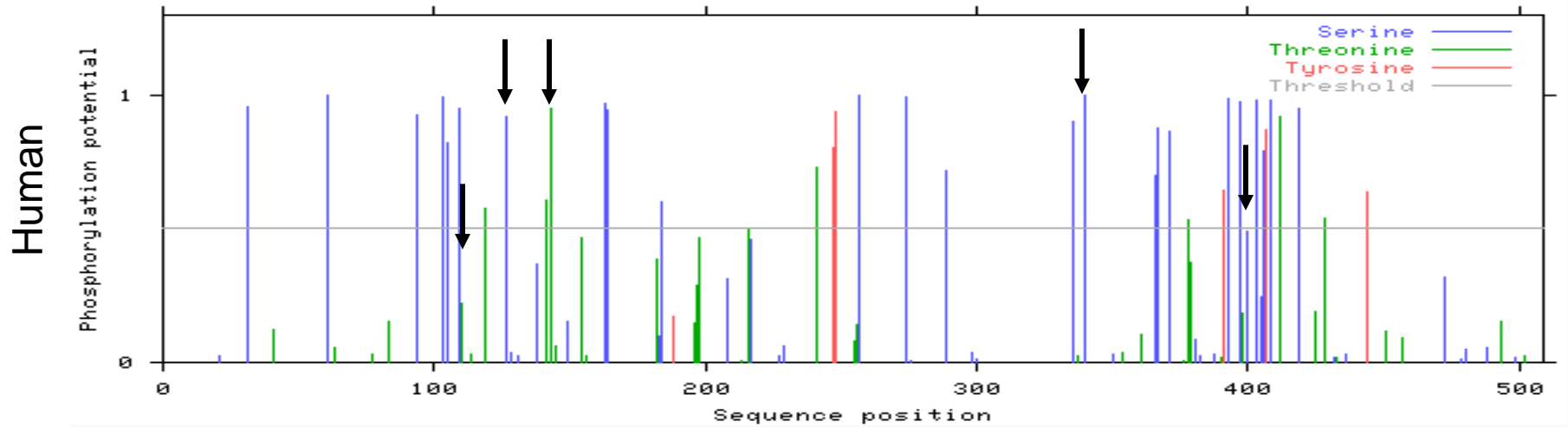
Curr Opin Cell Biol. 2008 December ; 20(6): 638–646

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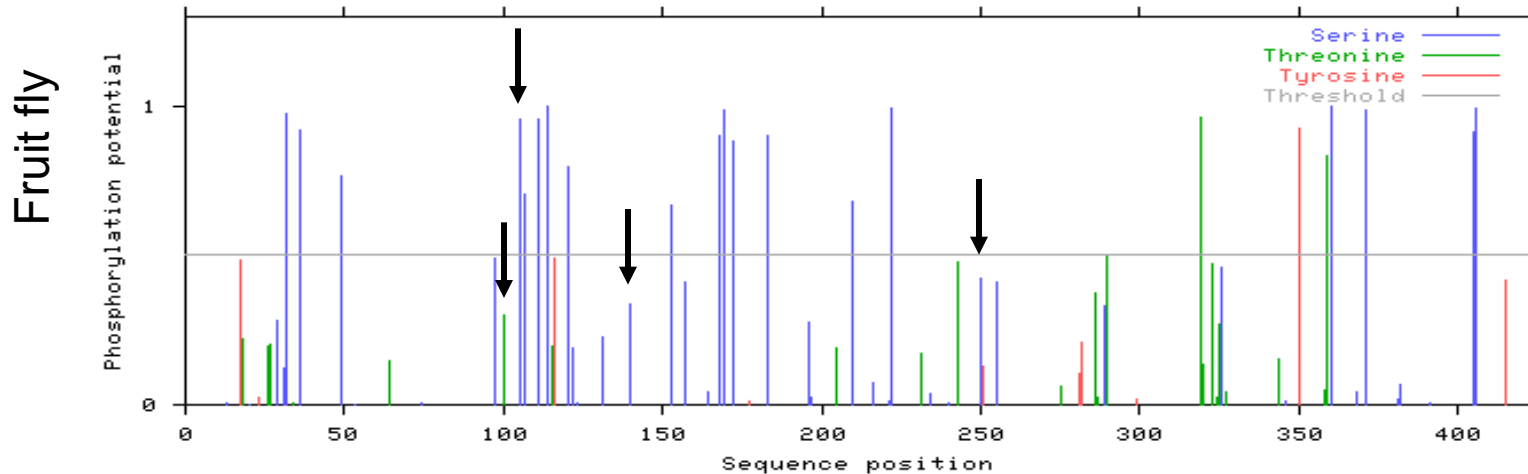
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NetPhos analysis phosphorylation sites

NetPhos 2.0: predicted phosphorylation sites in sp P46937 Y

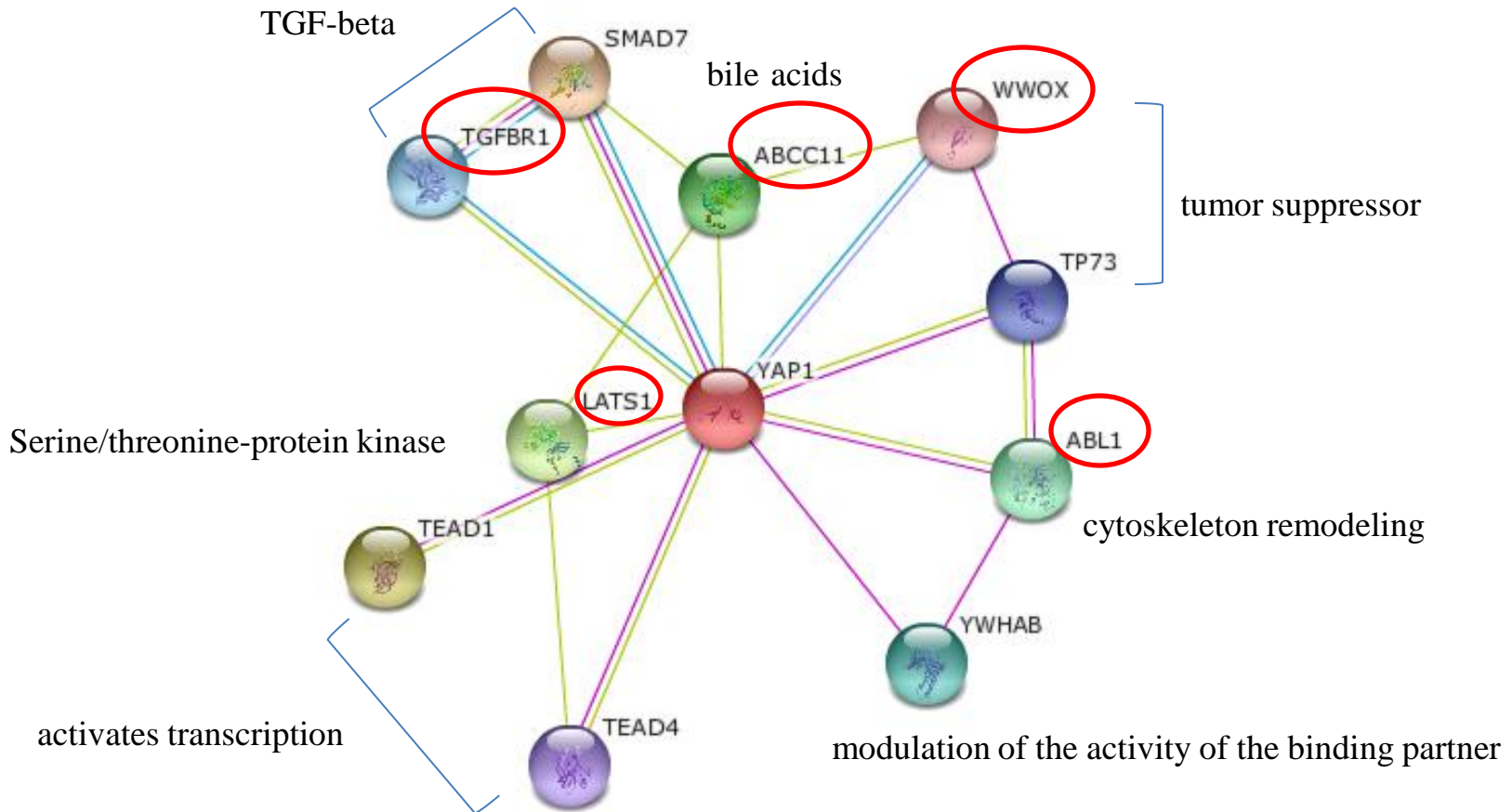


NetPhos 2.0: predicted phosphorylation sites in sp Q45VV3 Y



Post-translational modification of YAP

Modification Type	By	Sites	Fuction
Phosphorylation	LATS1/2	Ser-61/109/127/164/397	Cytoplasmic translocation and inactivation
	ABL1	Tyr-407	Enhances YAP1 stabilization
	CK1	Ser-400/403	Nucleu translocation and activation
Ubiquitination	SCF (beta-TRCP) E3 ubiquitin ligase		Degradation

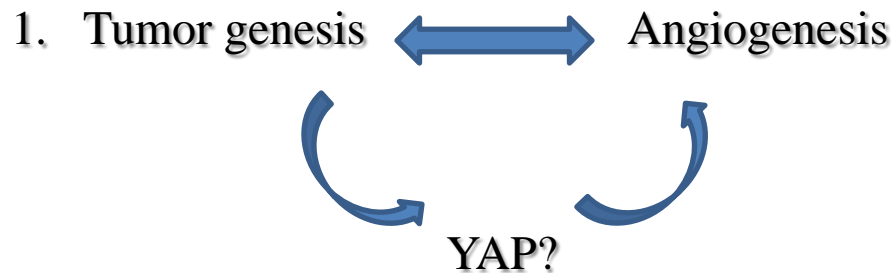


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Perspectives

YAP in Human Umbilical Vein Endothelial Cells(HUVECs)



HUVECs' abnormal functions ?

2. What role do YAP play in transducing mechanical stimulation signals in HUVECs?

**Thanks for
your attention!**

