

**Experiment title:**

Structural study of the TEAD4-YAP complex - an important Hippo pathway component involved in growth control

**Experiment number:**  
MX-877

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**Report:**

The Hippo signaling pathway controls cell growth, proliferation, and apoptosis by regulating the expression of target genes that execute these processes. Acting downstream of this pathway is the YAP transcriptional co-activator, whose biological function is mediated by the conserved TEAD family transcription factors. The interaction of YAP with TEADs is critical to regulate Hippo pathway-responsive genes. Here, we describe the crystal structure of YAP-interacting C-terminal domain of TEAD4 in complex with TEAD-interacting N-terminal domain of YAP. The structure reveals that the N-terminal region of YAP is folded into two short helices with an extended loop containing the PXXΦP motif in between, while the C-terminal domain of TEAD4 has an immunoglobulin-like fold. YAP interacts with TEAD4 mainly through the two short helices. Point mutations of TEAD4 indicate that the residues important for YAP interaction are required for its transforming activity. Mutagenesis reveals that the PXXΦP motif of YAP, although making few contacts with TEAD4, is important for TEAD4 interaction as well as for the transforming activity.

**Table 1. Data collection and refinement statistics**

Data collection	Se-Met TEAD4-YAP	Native TEAD4-YAP
Wavelength (Å)	0.9798	0.9796
Resolution limit (Å)	20-3.1	20-3.0
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Unit cell dimensions		
a, b, c (Å)	101.61, 148.09, 165.57	100.98, 146.91, 165.47
$\alpha$ , $\beta$ , $\gamma$ (°)	90, 90, 90	90, 90, 90
Unique reflections (N)	50744	58218
I/ $\sigma$	9.3(7.1)	9.5(2.5)
Completeness (%)	99.9(100.0)	99.9(100.0)
Redundancy	7.8(6.5)	3.6(3.7)
R <sub>merge</sub> <sup>a</sup>	0.09 (0.58)	0.06(0.30)
<b>Refinement</b>		
Resolution range (Å)		20-3.0
Used reflections (N)		47233
Nonhydrogen atoms (water)		7933(226)
R <sub>work</sub> <sup>b</sup> (%) / R <sub>free</sub> <sup>c</sup> (%)		23.3/28.8
R.m.s. deviations		
Bond lengths (Å)		0.01
Bond angles (°)		1.50
Ramachandran plot		
Most favored region		79.8%
Allowed region		18.1%
Generously allowed region		1.9%
Disallowed region		0.2%
Values in parentheses indicate the specific values in the highest resolution shell.		
<sup>a</sup> R <sub>merge</sub> = $\sum  I_j - \langle I \rangle  / \sum I_j$ , where I <sub>j</sub> is the intensity of an individual reflection, and $\langle I \rangle$ is the average intensity of that reflection.		
<sup>b</sup> R <sub>work</sub> = $\sum   F_o  -  F_c   / \sum  F_c $ , where F <sub>o</sub> denotes the observed structure factor amplitude, and F <sub>c</sub> denotes the structure factor amplitude calculated from the model.		
<sup>c</sup> R <sub>free</sub> is as for R <sub>work</sub> but calculated with 5.0% of randomly chosen reflections omitted from the refinement.		

**Reference:**

Chen L, Chan SW, Zhang X, Walsh M, Lim CJ, Hong W and Song H (2010) Structural basis of YAP recognition by TEAD4 in the Hippo pathway *Genes & Development*, 24, 290-300.



