Short Article

Structure

Palmitoylation of TEAD Transcription Factors Is Required for Their Stability and Function in Hippo Pathway Signaling

Highlights

- TEAD proteins are palmitoylated in human cells
- Palmitoylation is required for TEAD stability
- TEAD proteins do not stably associate with the nuclear envelope

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In Brief

Noland et al. report that TEAD transcription factors are palmitoylated. Structures of the palmitoylated YAP-binding domains of TEAD2 and TEAD3 are presented. Palmitoylation is required for TEAD stability, highlighting a novel form of regulation of the Hippo signaling pathway.

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Structure
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Palmitoylation of TEAD Transcription Factors Is Required for Their Stability and Function in Hippo Pathway Signaling

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SUMMARY

The Hippo signaling pathway is responsible for regulating the function of TEAD family transcription factors in metazoans. TEADs, with their co-activators YAP/TAZ, are critical for controlling cell differentiation and organ size through their transcriptional activation of genes involved in cell growth and proliferation. Dysregulation of the Hippo pathway has been implicated in multiple forms of cancer. Here, we identify a novel form of regulation of TEAD family proteins. We show that human TEADs are palmitoylated at a universally conserved cysteine, and report the crystal structures of the human TEAD2 and TEAD3 YAP-binding domains in their palmitoylated forms. These structures show a palmitate bound within a highly conserved hydrophobic cavity at each protein's core. Our findings also demonstrate that this modification is required for proper TEAD folding and stability, indicating a potential new avenue for pharmacologically regulating the Hippo pathway through the modulation of TEAD palmitoylation.

INTRODUCTION

The Hippo signaling pathway is a highly conserved kinase cascade that controls organ size and tissue homeostasis (Halder and Johnson, 2011; Zhao et al., 2011). The key downstream effectors include yes-associated protein (YAP) and its paralog, transcriptional co-activator with PDZ-binding motif (TAZ). These proteins interact with transcription factors in the nucleus to induce gene expression (Cao et al., 2008; Ota and Sasaki, 2008; Zhao et al., 2008). Upon Hippo pathway activation, Lats1/2 phosphorylates YAP, promoting its sequestration and inactivation in the cytoplasm by interaction with 14-3-3 proteins. Conversely, when this pathway is inactivated YAP is not phosphorylated and translocates into the nucleus, where it forms a complex with TEA domain (TEAD) transcription factors and co-activates the expression of multiple genes involved in cell fate determination, polarity, proliferation, and survival (Tian et al., 2010).

Defects in Hippo pathway regulation have been linked to uncontrolled cell proliferation and tumorigenesis (Harvey et al., 2013; Moroishi et al., 2015; Santucci et al., 2015). Multiple human cancers, including breast, liver, and pharyngeal cancers, show amplification or overexpression of the YAP gene (Liu et al., 2010; Overholtzer et al., 2006; Steinhardt et al., 2008; Zender et al., 2006). In addition, induced expression of YAP has been reported to trigger transformation of normal epithelial cells into metastatic cells (Overholtzer et al., 2006), and recent data have revealed that YAP is essential for the progression of pancreatic ductal adenocarcinoma in *Kras*-mutant mice (Kapoor et al., 2014). Since inhibition of the Hippo pathway leads to an activation of downstream genes, kinase components upstream of YAP phosphorylation are tumor suppressors, while YAP and TEAD, which together form a transcription co-activation complex, can promote cellular transformation. Understanding the regulation and interactions of these two proteins is therefore of critical importance to our understanding of tumorigenesis.

Crystal structures of the C-terminal YAP-binding domain (YBD) of TEAD1, TEAD2, and TEAD4 in the apo or co-activator bound states (Chen et al., 2010; Jiao et al., 2014; Li et al., 2010; Pobbati et al., 2012; Tian et al., 2010; Zhou et al., 2014) show that this domain adopts an immunoglobulin G-like fold, with two β sheets packing against each other to form a β sandwich capped with a pair of α helices (Figure 1A). The co-activator bound complex structures with YAP or vestigial-like proteins (Vgll) reveal that these proteins interact with TEAD via three distinct binding interfaces, with the majority of YAP-binding energy being driven by a short stretch of amino acids (YAP 86–100) that form a twisted-coil conformation, and bind onto a deep pocket centered around residue K289 in TEAD1.

Many proteins have been found to be regulated through S-palmitoylation, a highly conserved process occurring in all eukaryotic organisms that involves the attachment of 16-carbon fatty acids onto cysteine residues via a reversible thioester linkage (Chamberlain and Shipston, 2015; Hannoush, 2015). Palmitate