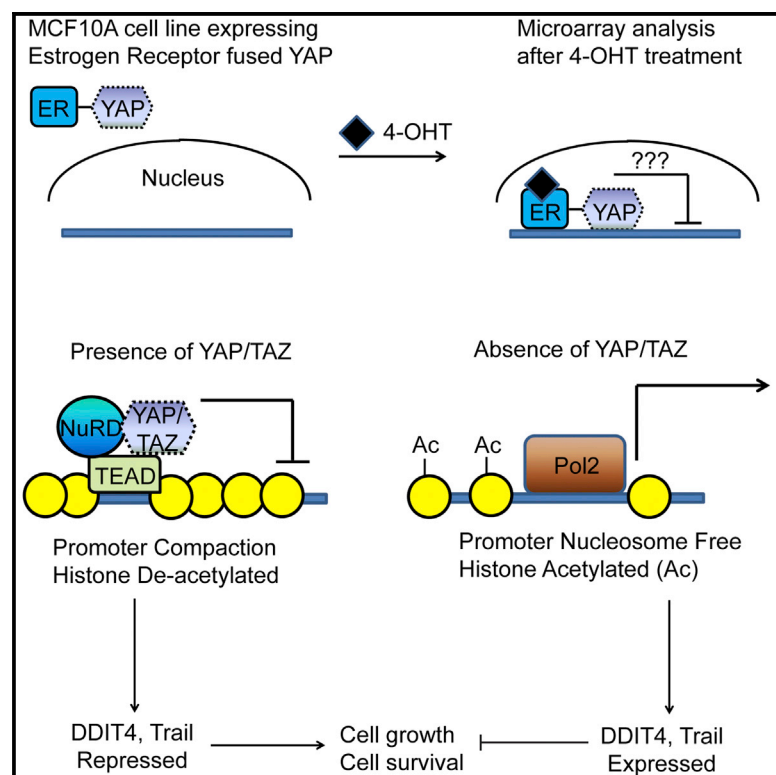


## Transcriptional Co-repressor Function of the Hippo Pathway Transducers YAP and TAZ

### Graphical Abstract



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### In Brief

YAP and TAZ are known as oncogenic transcriptional co-activators and key regulators of stem cell function. Here, Kim et al. show that YAP and TAZ can also function as transcriptional co-repressors to promote cell growth and survival, providing a new perspective for understanding the downstream outcome of YAP/TAZ activation.

### Highlights

- YAP/TAZ function as transcriptional co-repressors
- TEAD is required for target gene repression by YAP/TAZ
- The NuRD complex mediates repression of DDIT4 and Trail by YAP/TAZ-TEAD
- YAP/TAZ promote cell growth and survival by repressing DDIT4 and Trail

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# Transcriptional Co-repressor Function of the Hippo Pathway Transducers YAP and TAZ

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## SUMMARY

YAP (yes-associated protein) and TAZ are oncogenic transcriptional co-activators downstream of the Hippo tumor-suppressor pathway. However, whether YAP and/or TAZ (YAP/TAZ) engage in transcriptional co-repression remains relatively unexplored. Here, we directly demonstrated that YAP/TAZ represses numerous target genes, including tumor-suppressor genes such as *DDIT4* (DNA-damage-inducible transcript 4) and *Trail* (TNF-related apoptosis-inducing ligand). Mechanistically, the repressor function of YAP/TAZ requires TEAD (TEA domain) transcription factors. A YAP/TAZ-TEAD complex recruits the NuRD complex to deacetylate histones and alters nucleosome occupancy at target genes. Functionally, repression of *DDIT4* and *Trail* by YAP/TAZ is required for mTORC1 (mechanistic target of rapamycin complex 1) activation and cell survival, respectively. Our demonstration of the transcriptional co-repressor activity of YAP/TAZ opens a new avenue for understanding the Hippo signaling pathway.

## INTRODUCTION

YAP (yes-associated protein) and TAZ are potent oncogenic transcriptional co-activators that are opposed by the Hippo tumor-suppressor pathway. YAP is amplified in multiple forms of human cancers (Harvey et al., 2013). Overexpression of YAP and/or TAZ (YAP/TAZ) in normal epithelial cells induces cell transformation and confers a cancer stem cell phenotype (Cordeonsi et al., 2011; Overholtzer et al., 2006). Furthermore, YAP overexpression promotes hyperproliferation of tissue stem/progenitor cells and leads to cancer development in multiple epithelial tissues in mice (Camargo et al., 2007). YAP is crucial for cancer development induced by an Lkb1 deficiency,  $\beta$ -catenin activation, or oncogenic Ras mutation (Kapoor et al., 2014; Mohseni et al., 2014; Rosenbluh et al., 2012; Shao et al., 2014). Thus, one of the most important issues in the field is to identify target genes of YAP/TAZ that mediate their oncogenic activity. Since YAP/TAZ are regarded as transcriptional co-acti-

vators, many studies to date have focused on identifying genes upregulated by YAP/TAZ; several target genes, including CTGF (connective tissue growth factor), have been found (Zhao et al., 2008). While these genes explain some facets of the YAP overexpression phenotype, they do not fully account for YAP/TAZ function, suggesting that additional target genes remain to be discovered. An alternative explanation would be that YAP/TAZ repress expression of genes that inhibit cell growth or induce cell death. However, repressor functions of YAP/TAZ have been poorly investigated, with a single study suggesting that YAP/TAZ repress the expression of mesendoderm lineage genes in human embryonic stem (ES) cells (Beyer et al., 2013). Here, we have directly addressed whether YAP/TAZ can function as transcriptional co-repressors, demonstrating that they can function as oncogenes by repressing antiproliferative and cell-death-inducing genes.

## RESULTS

### YAP/TAZ Function as Transcriptional Co-repressors

To identify immediate target genes of YAP, we established an inducible system by fusing ERT2 (ligand binding domain of the estrogen receptor) to the N terminus of a constitutively active YAP S127/381A (YAP 2SA) mutant (Zhao et al., 2009) (Figure 1A). ERT2-fused proteins are normally inactive, but upon treatment with 4-OHT (4-hydroxytamoxifen), they rapidly translocate to the nucleus. ERT2-YAP 2SA was stably expressed in MCF10A cells followed by treatment with 4-OHT for 2 and 6 hr. As a control, we used 4-OHT-treated MCF10A cells expressing ERT2 only. ERT2-YAP 2SA had accumulated in the nucleus by 2 hr after 4-OHT treatment, as judged by both immunofluorescence and cell fractionation experiments (Figures S1A and S1B). ERT2-YAP 2SA was functionally active, as 4-OHT treatment robustly induced CTGF and Cyr61, which are two well-established targets of YAP (Figures S1C and S1D). Notably, ERT2-YAP 2SA was markedly stabilized by 6-hr post-treatment with 4-OHT (lane 6; Figure S1C).

Microarray analyses revealed that ~100 genes were acutely suppressed (>2-fold) following 4-OHT treatment in ERT2-YAP 2SA cells (Figure 1B; Table S1). Interestingly, these downregulated genes included some tumor suppressor genes, such as *DDIT4* (DNA-damage-inducible transcript 4), *Trail* (TNF-related apoptosis-inducing ligand), and *TSC22D* (TGF $\beta$ -stimulated clone

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