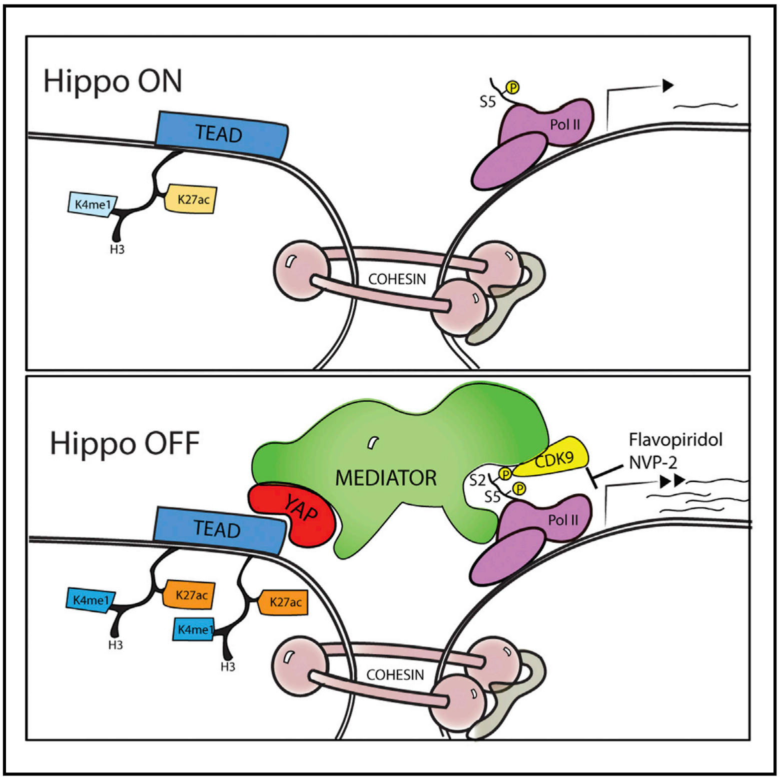
Short Article

Molecular Cell

YAP Drives Growth by Controlling Transcriptional Pause Release from Dynamic Enhancers

Graphical Abstract



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In Brief

The transcriptional coactivators YAP and TAZ are critical regulators of stem cell activity and tumorigenesis. Galli et al. show that YAP/TAZ binding is restricted to a relatively small number of the most potent enhancers in the genome. They show that YAP/TAZ regulate transcriptional elongation from these elements by recruiting the Mediator complex.

Highlights

- YAP/TAZ binding is restricted to a subset of distal regulatory regions in the genome
- YAP/TAZ occupancy confers potent transcriptional activity to superenhancer regions
- YAP/TAZ regulate transcriptional elongation
- YAP recruits the Mediator complex and CDK9-elongating kinase

Accession Numbers

GSE62275

Galli et al., 2015, Molecular Cell *60*, 1–10
October 15, 2015
http://dx.doi.org/10.1016/j.molcel.2015.09.001

Please cite this article in press as: Galli et al., YAP Drives Growth by Controlling Transcriptional Pause Release from Dynamic Enhancers, Molecular Cell (2015), http://dx.doi.org/10.1016/j.molcel.2015.09.001

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YAP Drives Growth by Controlling Transcriptional Pause Release from Dynamic Enhancers

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SUMMARY

The Hippo/YAP signaling pathway is a crucial regulator of tissue growth, stem cell activity, and tumorigenesis. However, the mechanism by which YAP controls transcription remains to be fully elucidated. Here, we utilize global chromatin occupancy analyses to demonstrate that robust YAP binding is restricted to a relatively small number of distal regulatory elements in the genome. YAP occupancy defines a subset of enhancers and superenhancers with the highest transcriptional outputs. YAP modulates transcription from these elements predominantly by regulating promoter-proximal polymerase II (Pol II) pause release. Mechanistically, YAP interacts and recruits the Mediator complex to enhancers, allowing the recruitment of the CDK9 elongating kinase. Genetic and chemical perturbation experiments demonstrate the requirement for Mediator and CDK9 in YAP-driven phenotypes of overgrowth and tumorigenesis. Our results here uncover the molecular mechanisms employed by YAP to exert its growth and oncogenic functions, and suggest strategies for intervention.

INTRODUCTION

At the core of the Hippo pathway, a network of kinases controls the subcellular localization of the transcriptional coactivator YAP and its paralogue TAZ (Ramos and Camargo, 2012). YAP/TAZ can translocate into the nucleus to activate gene expression by associating with a number of DNA-binding transcription factors, particularly of the TEAD family (Zhao et al., 2008). Ablation of Hippo signaling or forced expression of constitutively active YAP results in increased organ size, expansion of tissue progenitor compartments, and, ultimately, occurrence of cancers (Benhamouche et al., 2010; Camargo et al., 2007; Dong et al., 2007; Zhou et al., 2009). The remarkable effects of Hippo/YAP on organ growth and its potential to crosstalk with multiple oncogenic signaling cascades (Barry et al., 2013; Kapoor et al., 2014) make this pathway a very attractive target for cancer therapeutics. However, despite the tremendous importance of YAP/TAZ in developmental and disease biology, major gaps in our mechanistic understanding of the transcriptional function of YAP remain. For instance, it is still unclear where YAP, TAZ, and TEADs bind in the genome of cancer cells, as is the identity of the transcriptional complexes that are recruited by these factors to drive gene transcription.

The transcriptional state of a specific cell type is determined by the wiring of transcription factor networks that occupy a variety of genomic elements dispersed throughout the noncoding area of the genome. Such elements are able to impede (named insulators) (Wendt et al., 2008), or to drive transcription (named enhancers) of distal genes by recruiting a number of cell-type-specific transcription factors (Calo and Wysocka, 2013). Enhancers are known to be the major determinants of cell-type- and cancer-type-specific gene expression program (Akhtar-Zaidi et al., 2012; Heintzman et al., 2009). More recently, a very restricted subset of enhancers, named "superenhancers," has been shown to drive higher transcription rate of genes that define cell identity (Hnisz et al., 2013), and of key oncogenic drivers in cancer cells (Lovén et al., 2013).

Mediator is a large multisubunit complex which binds to enhancer elements and, together with the structural complex cohesin, is involved in bringing distal elements in close proximity to target promoters (Kagey et al., 2010). Mediator is able to regulate both basal transcription driven by RNA Pol II as well as recruitment of CDK9 to boost transcriptional elongation by releasing Pol II promoter pausing (Malik and Roeder, 2010). Such function, coupled to the binding of Mediator to a variety of cell-type-specific transcription factors, allows Mediator to integrate multiple signaling cues to deliver appropriate transcriptional activation (Malik and Roeder, 2010).

Here we utilize multiple genomic technologies and biochemistry to provide a mechanistic insight into YAP/TAZ-driven transcription. We demonstrate that in cancer cells, YAP/TAZ occupy a very restricted number of TEAD positive enhancers