



Available online at www.sciencedirect.com

ScienceDirect

journal homepage: <http://ees.elsevier.com/gendis/default.asp>



RESEARCH WATCH

Wnt *versus* Hippo: A balanced act or dynamic duo?

Zhongliang Wang, Jixing Ye, Youlin Deng, Zhengjian Yan, Sahitya Denduluri, Tong-Chuan He*

Molecular Oncology Laboratory, The University of Chicago Medical Center, Chicago, IL 60637, USA

Received 2 September 2014; accepted 3 September 2014

Available online 16 September 2014

KEYWORDS

β -TrCP;
Destruction complex;
Hippo;
Proteasome
degradation;
Signal transduction;
Wnt/ β -catenin;
YAP/TAZ

Abstract The Hippo signaling pathway was first discovered in *Drosophila* as a conserved regulator of organ size. Genetic inactivation in mice demonstrates that the Hippo pathway functions as a fundamental inhibitor of organ growth during development, and as a critical tumor suppressor in epithelial tissues.

Copyright © 2014, Chongqing Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

The Hippo signaling pathway was first discovered in *Drosophila* as a conserved regulator of organ size. Genetic inactivation in mice demonstrates that the Hippo pathway functions as a fundamental inhibitor of organ growth during development, and as a critical tumor suppressor in epithelial tissues.¹ The prototype pathway consists of a serine/threonine kinase cascade regulated by the tumor suppressor Hippo (Mst1 and Mst2 in mammals) and the downstream oncoprotein Yki in *Drosophila* (YAP and TAZ in mammals), which transcriptionally activates target genes and regulates cell proliferation, cell survival, differentiation, cell polarity, and mechanotransduction.¹ Like other

well-known signaling pathways, the Hippo pathway relays signals from the plasma membrane into the nucleus. However, this pathway does not have dedicated extracellular signaling molecules and/or receptors. Increasing evidence shows that the core Hippo kinase cascade integrates multiple upstream signaling inputs, and that actin cytoskeleton or cellular tension appears to be the master mediator, integrating and transmitting upstream signals to the core Hippo signaling cascade.

An earlier study showed that the Hippo pathway may restrict Wnt/ β -catenin signaling by promoting an interaction between TAZ and Disheveled (DVL) in the cytoplasm, inhibiting CK1 δ/ϵ -mediated phosphorylation of DVL.² However, it has been recently reported that YAP forms a transcriptional complex with β -catenin and TBX5, and that the β -catenin-YAP-TBX5 complex drives cell survival and oncogenesis.³ TAZ was also shown to serve as a

* Corresponding author.

E-mail address: tche@bsd.uchicago.edu (T.-C. He).

Peer review under responsibility of Chongqing Medical University.

downstream mediator of Wnt/ β -catenin signaling in a Hippo-independent fashion.⁴ Thus, the Hippo transducers YAP/TAZ have been reported to play positive, as well as negative, roles in Wnt signaling.

A recent study published in *Cell* may provide further insight into the mechanisms through which YAP/TAZ may orchestrate the Wnt response.⁵ In the presence of Wnt, it has been shown that YAP/TAZ proteins are released from the destruction complex, allowing for nuclear accumulation and driving Wnt/YAP/TAZ-dependent biological effects.⁵ Without Wnt, YAP/TAZ are transcriptionally inactivated by sequestration in the destruction complex through binding to Axin1, causing β -TrCP recruitment to the destruction complex and subsequent β -catenin degradation. On the other hand, when Wnt is present, YAP/TAZ proteins are released from the destruction complex and β -TrCP recruitment cannot occur; this is essential for Wnt/ β -catenin signaling.⁵ Mechanistically, YAP/TAZ and LRP6 compete for the same domain of Axin – to the extent that the association of Axin to YAP/TAZ is incompatible with Axin-LRP6 association. Thus, Axin/YAP/TAZ complexes dominate in Wnt-OFF cells, whereas Axin/LRP6 complexes dominate in Wnt-ON cells. Wnt signaling physically dislodges YAP/TAZ from the destruction complex, causing them to undergo nuclear accumulation and activate expression of target genes. Accordingly, it was shown that cytoplasmic, but not nuclear, YAP/TAZ are β -catenin inhibitors. Furthermore, YAP/TAZ are required for crypt regeneration and *Apc* deficiency-induced intestinal crypt overgrowth.⁵ Taken together, these biochemical, functional, and genetic findings strongly suggest that YAP and

TAZ may be integral components of the β -catenin destruction complex, which serves as a cytoplasmic sink for YAP/TAZ. Nonetheless, the precise role of Hippo in Wnt signaling remains to be fully understood, as YAP1 or TAZ knockout animals do not phenocopy the loss of Wnt signaling.¹

Acknowledgments

The authors declare no conflict of interest. Work in the corresponding author's laboratory was supported in part by research grants from the National Institutes of Health (AT004418 and CA106569 to TCH).

References

1. Johnson R, Halder G. The two faces of Hippo: targeting the Hippo pathway for regenerative medicine and cancer treatment. *Nat Rev Drug Discov.* 2014;13(1):63–79.
2. Varelas X, Miller BW, Sopko R, et al. The Hippo pathway regulates Wnt/ β -catenin signaling. *Dev Cell.* 2010;18(4):579–591.
3. Rosenbluh J, Nijhawan D, Cox AG, et al. Beta-Catenin-driven cancers require a YAP1 transcriptional complex for survival and tumorigenesis. *Cell.* 2012;151(7):1457–1473.
4. Azzolin L, Zanconato F, Bresolin S, et al. Role of TAZ as mediator of Wnt signaling. *Cell.* 2012;151(7):1443–1456.
5. Azzolin L, Panciera T, Soligo S, et al. YAP/TAZ incorporation in the β -catenin destruction complex orchestrates the Wnt response. *Cell.* 2014;158(1):157–170.