YAP/TAZ Join the Play with β-catenin to Orchestrate Wnt Signaling

Noushin Nabavi
Department of Cellular and Molecular Pharmacology. University of California San Francisco, 600 16th Street, MC 2140, CA 94158-2140, USA
Email: Noushin.nabavi@ucsf.edu

Abstract
For the purpose of studying Wnt signaling, the intestinal epithelium has been the most relevant biological tissue for its differential topology expression of Wnt signaling: active in all crypt cells (helping in proliferation, stemness, regeneration, and tissue homeostasis) and inactive in the villi cells. Interestingly though, YAP/TAZ regulation through Wnt signaling has been more controversial and the subject of this review. Recent work shows that Wnt signaling inactivates the cytoplasmic pool of destruction complex through dissociating β-TrCP E3 ligase from the complex. Further, in addition to β-catenin, YAP and TAZ, two related proteins known for their roles in the Hippo signaling cascade, are two other pivotal regulators of cell proliferation and stemness during organ growth, regeneration, and tumorigenesis. The biological function of YAP/TAZ and β-catenin overlap to suggest that these factors are not completely independent of one another and may influence each other's activities.

Keywords: β-catenin, Hippo Signaling, proliferation, tumorigenesis, YAP/TAZ, Wnt signaling

Yorkie-homologues (Yes-associated protein) YAP and TAZ (transcriptional coactivator with PDZ-binding motif, also known as WWTR1) are two of the key molecular players in the Hippo pathway promoting tissue proliferation, stem cell renewal, and organ growth through nuclear localization and transcriptional regulation[7]. The Hippo signaling pathway has been classified as an important player in organ size control and tumorigenesis[8].

The Wnt signaling pathway on the other hand is regulated by the binding of Wnt ligand to a Frizzled protein receptor which then passes the biological signals to the protein Dishevelled (Dsh) inside the cell. There are three identified Wnt pathways each responsible for certain biological activities: canonical Wnt pathway leads to regulation of gene transcription, the noncanonical pathway regulates the cytoskeleton that is responsible for cell shape, and the noncanonical Wnt/calcium pathway which regulates calcium concentrations inside the cell[2]. For the purpose of this article, we are going to consider the canonical Wnt signaling pathway in more depth. Without Wnt signaling, the cytosolic destruction complex degrades β-catenin. The destruction complex is composed of three main protein components: Axin, Adenomatosis Polyposis Coli (APC), and Glycogen Synthase Kinase 3 (GSK3) among others. In the presence of Wnt, β-catenin gets disassembled from the destruction complex and is translocated to the nucleus to regulate transcription of downstream genes[9]. More interestingly, a recent article by Byun et al has shown that the canonical Wnt signaling pathway as evidenced in the osteogenic differentiation process can regulate TAZ. They show that Wnt3 increases TAZ expression and facilitate its dephosphorylation that can then stabilize TAZ and promote its translocation to the nucleus for downstream transcriptional regulation[10]. In addition, Imajo et al identified a novel mechanism through which YAP/TAZ of Hippo signaling pathway antagonize Wnt signaling through preventing β-catenin translocation to the nucleus for further transcriptional regulation[12].

However, how YAP/TAZ are exactly regulated are not as clearly understood. In their article, Azzolin et al[1] validate the hypothesis that YAP/TAZ are integral factors of the destruction complex

through biochemical, genetic, and functional evidence. In fact, they find that YAP and TAZ mRNAs are both expressed in crypt and villi cells whereas the protein levels are only prominent in the crypt compartment indicating a posttranscriptional regulation of YAP/TAZ. Interestingly, YAP/TAZ deficiencies showed no consequences on proliferation of crypt cells and intestinal architecture. However, they have previously been shown to regulate organ size and tumorigenesis through the Hippo pathway[4].

To further elucidate the role of these two molecules, Azzolin et al first show that YAP/TAZ are transcriptionally inactivated by sequestration in the destruction complex using HEK293 cells. They immunoprecipitated Axin1, the rate limiting molecule for destruction complex assembly, and found that along with Axin1 interaction with the usual suspects (β-catenin, GSK3β, and β-TrCP), YAP/TAZ also interact with Axin1. This observation was also true in the reverse order, immunoprecipitating YAP/TAZ resulted in finding the same interacting partners. To elucidate the function of the complex assembly, the authors knocked down Axin1/2 and APC and subsequently found that YAP/TAZ accumulated in the nucleus. From these data, they concluded that YAP/TAZ incorporation in the destruction complex acts as its cytoplasmic anchor causing transcriptional inactivation.

In the absence of Wnt signaling, the destruction complex efficiently captures the cytosolic β-catenin and phosphorylates it with GSK3, which leads to its ubiquitination by the β-TrCP ubiquitin ligase and subsequent degradation through the proteasomal pathway. In the presence of Wnt signaling, the destruction complex gets functionally inactivated causing the escape of β-catenin from degradation and its ultimate accumulation and entry in the nucleus (Figure 1).

To study how Wnt signaling impacts YAP/TAZ, Azzolin et al found that upon Wnt stimulation, the YAP/TAZ association with Axin1 was decreased whereas Axin1 association with LRP6 increased. Therefore, it seems that YAP/TAZ and LRP6 are in competition to bind to Axin1 to form a complex. Azzolin et al tested this hypothesis through immunoprecipitation of full length and truncated Axin1 and found that YAP can bind and be pulled down with the full length Axin1, similar to LRP6. In addition, increasing the expression of LRP6 in HEK293 cells resulted in decrease association of YAP/TAZ complex with Axin1 in Wnt-ON cells and dissociation of destruction complex. Similarly, in Wnt-OFF cells, the destruction complex of YAP/TAZ forms in the cytoplasm and in turn inhibits their accumulation and transcriptional activity in the nucleus. Therefore, although YAP/TAZ is indispensible for intestinal homeostasis, they are integral components of the destruction complex required for regulating Wnt signaling. More specifically, YAP/TAZ are important for anchoring β-catenin in its phosphorylated form in the destruction complex of cytosol and inhibit its transcriptional activity in the nucleus in Wnt-OFF states. Upon stimulation of Wnt to Wnt-ON state, both β-catenin and YAP/TAZ translocate to the nucleus for transcriptional activation of target genes.

In light of this research, we can envision not only the well-characterized β-catenin but also YAP/TAZ to be important players in Wnt signaling pathway.

Since YAP/TAZ have been classically associated with the Hippo pathway, the authors also hypothesis and explore the connection of Hippo and Wnt signaling pathways by proposing that the YAP/TAZ nuclear accumulation in inactivated Hippo pathway state diverts them away from the cytosolic destruction complex and as a result β-catenin is no longer anchored and free to accumulate in the nucleus and turn on Wnt pathway. Also, finding the important of TAP/TAZ in proliferation of oncogenic cells and not in normal stem cells has specific implications in the cancer field and designing drug therapeutics that target these molecules specifically[6].

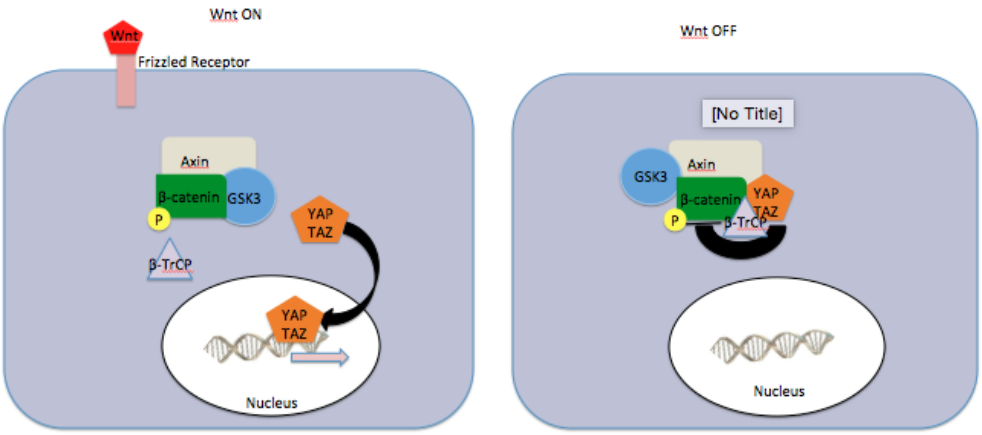

Figure 1. Schematic representation of YAP/YAZ incorporation into the destruction complex in Wnt ON and OFF states

Acknowledgments

I would like to thank the anonymous reviewers for their thoughtful suggestions for improving this article.

References

1. Azzolin L, Panciera T, Soligo S, Enzo E, Bicciato S, Dupont S, Bresolin S, Frasson C, Basso G, Guzzardo V, Fassina A, Cordenonsi M, Piccolo S. YAP/TAZ Incorporation in the β-Catenin Destruction Complex Orchestrates the Wnt Response. *Cell* 158, 2014: 157-170.

2. Joshua T. Morgan, Christopher J. Murphy, Paul Russell. What do mechanotransduction, Hippo, Wnt, and TGFβ have in common? YAP and TAZ as key orchestrating molecules in ocular health and disease, Experimental Eye Research, 2013, Volume 115, Pages 1-12

3. Ryouhei Tsutsumi, Mohammad Masoudi, Atsushi Takahashi, Yumiko Fujii, Takeru Hayashi, Ippei Kikuchi, Yumeko Satou, Masanori Taira, Masanori Hatakeyama. YAP and TAZ, Hippo Signaling Targets, Act as a Rheostat for Nuclear SHP2 Function, Developmental Cell, 2013, Volume 26, Issue 6, Pages 658-665

4. Zhao B, Li L, Lei Q, Guan KL. The Hippo-YAP pathway in organ size control and tumorigenesis: an updated version. *Genes Dev, 2010,* 24: 862–874

5. Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, Xie J, Ikenoue T, Yu J, Li L, Zheng P, Ye K, Chinnaiyan A, Halder G, Lai ZC, Guan KL. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. *Genes Dev, 2007,* 21: 2747–2761

6. Moon RT, Kohn AD, De Ferrari GV, Kaykas A. WNT and beta-catenin signalling: diseases and therapies. *Nat Rev Genet*, 2004, 5: 691–701

7. Sirio Dupont, Leonardo Morsut, Mariaceleste Aragona, Elena Enzo, Stefano Giulitti, Michelangelo Cordenonsi, Francesca Zanconato, Jimmy Le Digabel, Mattia Forcato, Silvio Bicciato, Nicola Elvassore & Stefano Piccolo. Role of YAP/TAZ in mechanotransduction. Nature, 2011, 474, 179-183

8. Bin Zhao, Li Li, Qunying Lei, and Kun-Liang Guan. The Hippo–YAP pathway in organ size control and tumorigenesis: an updated version. Genes & Dev. 2010, 24: 862-874

9. Stamos JL1, Weis WI. The β-catenin destruction complex. Cold Spring Harb Perspect Biol. 2013 Jan 1;5(1)

10. M R Byun, J-H Hwang, A R Kim, K M Kim, E S Hwang, M B Yaffe and J-H Hong. Canonical Wnt signalling activates TAZ through PP1A during osteogenic differentiation. Cell Death & Differentiation, 2014, 21, 854-863.

11. Masamichi Imajo,1,2 Koichi Miyatake,1 Akira Iimura,1 Atsumu Miyamoto,1 and Eisuke Nishida. A molecular mechanism that links Hippo signalling to the inhibition of Wnt/β-catenin signalling. EMBO J., 2012, 31(5): 1109-1122.