Have you seen?

Transcription and processing: multilayer controls of RNA biogenesis by the Hippo pathway

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The Hippo pathway plays a critical role in organ size control and tumorigenesis. YAP (and also its homologue TAZ) is a transcription co-activator that mediates the biological functions of the Hippo pathway. YAP activity is inhibited upon phosphorylation by the Lats kinases (reviewed in Yu & Guan, 2013). In a recent study in Cell, Mori et al (2014) uncover a new function of YAP in global microRNA (miRNA) biogenesis by the modulation of the Microprocessor machinery. The results also suggest that this novel YAP function may contribute to cell growth control and tumorigenesis.

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YAP inactivation is involved in cell–cell contact inhibition. When cells are cultured at low density, YAP localizes to the nucleus to regulate gene expression; in contrast, under high cell density, YAP remains inactive in the cytoplasm (Fig 1A and B; Zhao et al, 2007). miRNA biogenesis is also affected by cell–cell contact, with increasing levels of mature miRNAs in cells cultured at high density (Hwang et al, 2009). The new paper by Mori et al (2014) nicely connects these so far separate observations to report that YAP acts upstream in the process of miRNA biogenesis and is crucial for miRNA expression in response to cell–cell contact signals. In the absence of cell contact-mediated signals, nuclear YAP interacts with DDX17 (DEAD Box Helicase 17, also known as p72), which sequesters DDX17 away from DROSHA and DGCR8 (two major components of the Microprocessor). DDX17 recognizes a sequence motif in the 3′ flanking sequence of pri-miRNAs, and this facilitates cleavage by Microprocessor. When DDX17 is associated with YAP, the processing of pri-miRNA to pre-miRNA by Microprocessor is reduced, limiting overall miRNA production (Fig 1A). Cell contact-induced cytoplasmic retention of YAP prevents DDX17 binding and permits DDX17 interaction with DROSHA and DGCR8 to mediate effective pri-miRNA cleavage and miRNA production (Fig 1B).

YAP is a transcription co-activator, which modulates gene expression by interacting with transcription factors such as TEAD1-4 (Fig 1C). It is believed that YAP exerts its biological functions by regulating the transcription of genes involved in cell proliferation and cell death (Yu & Guan, 2013). YAP can directly induce expression of some miRNAs such as miR-29 (Tumaneng et al, 2012). The novel findings by Mori et al now suggest an even broader, regulatory role of YAP by functioning as a master regulator for miRNA processing. Additionally to its described effect in regulating miRNA and miRNA transcription, YAP appears to regulate miRNA processing in a transcription-independent manner. Indeed, one could infer that YAP-regulated miRNAs may form a regulatory loop by modulating the stability or translation efficiency of mRNAs induced by YAP and other transcription factors (Fig 1C). It’s, however, noteworthy that some findings in Mori et al (2014) are not consistent with a recent report (Chauilk et al, 2014) suggesting some mature miRNAs being rather negatively correlated with cell density, and YAP induces the activity of DICER complex to enhance the processing of pre-miRNAs to mature miRNAs (Fig 1C). Though further studies would be needed to clarify these differences, one simple explanation is that YAP may induce processing of some while inhibit other pre-miRNAs.

A global repression of miRNA expression is frequently observed in many different types of cancers (Lu et al, 2005); however, it’s not clear what contributes to the miRNA biogenesis defects in cancers. Mori et al (2014) link YAP activation and miRNA repression in cancers, which is consistent with an oncogenic role of YAP. Using genetic tools, Mori et al (2014) demonstrate that miRNA production is decreased in cells with high YAP activity and also in YAP-driven tumors, and the miRNA repression results in the activation of oncoproteins such as MYC, suggesting an important role of miRNA biogenesis in YAP-induced tumorigenesis.

Further, the down-regulation of miRNA processing can play a causative role in tumorigenesis. As one example, depletion of Microprocessor components or the DICER complex leads to cellular transformation (Kumar et al, 2007). It is therefore reasonable to speculate that YAP induces tumorigenesis via global miRNA suppression. Previously, it has been shown that the YAP-TEAD binding is critical for YAP-induced cell transformation, and a YAP-TEAD binding-defective YAP mutant (S94A) failed to transform NIH3T3 cells (Zhao et al, 2009). In addition, a dominant-negative TEAD completely abrogates the tumor-promoting effect of YAP in mice liver (Liu-Chittenden et al, 2012). These data...
suggest an essential role of YAP-TEAD interaction and its transcriptional output on tumorigenesis. In contrast, Mori et al (2014) suggest additional, transcription-independent mechanisms for YAP, based on a YAP mutant (S94A) that effectively represses miRNA expression. Thus, it would be critical to assess the importance of YAP-DDX17 interaction and the transcription-independent miRNA biogenesis in the biology controlled by the Hippo pathway. For instance, does DDX17 function as a bona fide tumor suppressor? Is DDX17 involved in organ size control downstream of the Hippo pathway? Answers to these questions will be critical to corroborate the broader significance of these new and really intriguing findings.

The rather unexpected discoveries by Mori et al (2014) and Chaulk et al (2014) indicate a crucial role of YAP not only in the expression of mRNAs but also as a regulator in microRNA processing. There is no doubt that these results widen our understanding of the Hippo pathway. The exact function of the multitude of YAP target genes for its respective biological effects is far from being fully understood. One may speculate that both the genes directly induced by YAP and those from its new involvement in miRNA processing collectively contribute to the physiological output of YAP and the Hippo pathway.

Conflict of interest
The authors declare that they have no conflict of interest.

References


