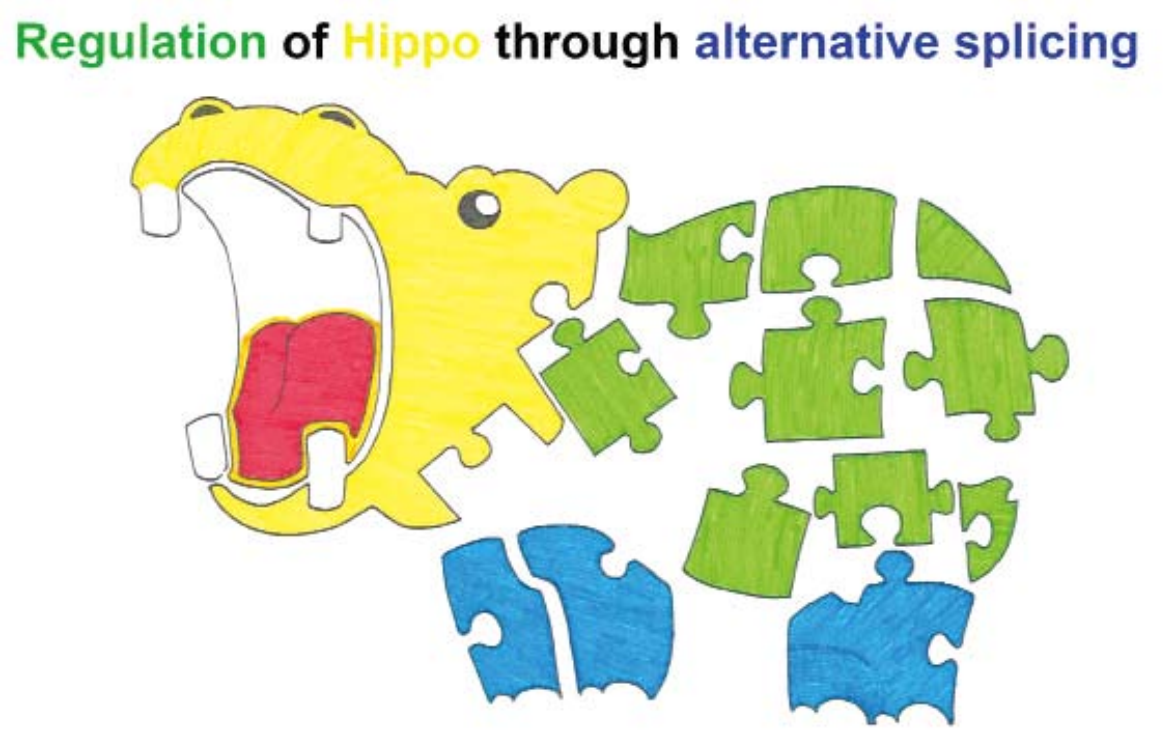
This Old Hippo Has a New Trick — New Regulatory Mode of Hippo-YAP Pathway Inspires Unconventional Cancer Therapy

Hippo-YAP (Yes-associated protein) signaling is a key pathway that regulates cell proliferation and organ size, whose mis-regulation is closely associated with human cancer. In a recent *Nature Communications* paper, Dr. WANG Zefeng's group from the CAS-MPG Partner Institute for Computational Biology (PICB), Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS) and his collaborators from Dalian Medical University reported that Hippo-YAP pathway, which is altered in many cancers to amplify proliferative signals, can be controlled at RNA level through alternative splicing.

This is the first report that Hippo-YAP pathway is regulated through RNA splicing, which probably exemplify a new general regulatory mode of cell proliferation at RNA level.

According to the current model, the activity of Hippo-YAP pathway is mainly controlled through protein phosphorylation and degradation. In this new study, researchers have found that one important effector



This figure illustrates the regulation of Hippo through alternative splicing. (Image: by Dr. WANG Zefeng's Lab)

of Hippo-YAP pathway, TEAD4 (TEA domain family member), is under control by alternative splicing. Through this new splicing switch, a truncated isoform of canonical TEAD4, TEAD4-S, will be produced, which lacks N-terminal DNA-binding domain, but contains YAP-interaction domain. Therefore, TEAD4-S suppresses the translocation of YAP from cytoplasm to nucleus, and thus acts as a dominant negative isoform to YAP activity. Through this mechanism, overexpression of TEAD4-S suppresses proliferation and migration of cancer cells, as well as inhibits tumor growth in xenograft mouse model. Furthermore, the researchers showed that splicing of TEAD4-S is facilitated by the tumor suppressor RBM4 (RNA-binding protein 4). Consistently, TEAD4-S is reduced in human cancers, which might be able to explore as a new anti-cancer strategy because patients with elevated TEAD4-S levels have an improved survival rate.

Under normal condition, YAP is translocated into nucleus to promote cell growth; however the activation of Hippo causes YAP phosphorylation, leading to cytoplasmic retention and degradation of YAP. Because YAP lacks a DNA binding domain, the activity of YAP has to be mediated by transcription factor TEAD proteins that specifically recruit YAP to DNA to stimulate cell proliferation.

Altogether these data reveal a splicing switch that serves to fine-tune Hippo-YAP pathway. Intriguingly, some key components of Hippo-YAP pathway undergo extensive regulation at RNA level through alternative splicing. However the biological functions of these isoforms are unclear. Alternative splicing is a key mechanism to increase coding complexity of human genome, and alternation of splicing is a major hallmark of cancer. It is expected that splicing mis-regulations of other genes in Hippo-YAP pathway also play critical roles in cancer development and thus should be explored as a new route of potential cancer therapy.

This finding was published in Nature Communications on June 13, 2016, in an article titled “A splicing isoform of TEAD4 attenuates the Hippo-YAP signalling to inhibit tumour proliferation”.

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