

## Correlation between Hippo-YAP signaling pathway and liver cancer

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**Abstract.** The Hippo signaling pathway is a pathway that inhibits cell growth and controls organ size primarily by regulating cell proliferation and apoptosis. Cancer has long been considered by humans to be the "number one killer" and is known as an incurable disease. Among them, liver cancer is one of the malignant tumors that seriously threaten people's health. Therefore, it is particularly important to develop effective early diagnostic markers and therapeutic targets for liver cancer. This article reviews the composition and function of Hippo-YAP signaling pathway and its correlation between liver cancer, aiming at the early diagnosis of liver cancer, improving the specificity and targeting of liver cancer treatment, and reducing the damage to chemotherapy drugs to normal stem cells. The mechanism of drug resistance to liver cancer provides an effective basis and plays a role in assessing prognosis.

### 1. Introduction

Hippo signaling pathway has been discovered in *Drosophila* in recent years, which regulates cell size by regulating cell proliferation and apoptosis<sup>[1]</sup>. Abnormal regulation of this pathway can lead to a variety of diseases, that is, when this dynamic balance is destroyed, it can lead to excessive cell proliferation or inhibition of apoptosis, resulting in unrestricted growth of tissues and organs or malignant transformation of cells<sup>[2]</sup>. It has been found that the Hippo-YAP pathway is an important pathway for the regulation of liver cancer formation in numerous signaling pathways<sup>[3]</sup>. YAP is the core effector of Hippo pathway, which plays an important role in intracellular signaling and transcriptional regulation. Hippo-YAP signaling pathway can regulate the growth and development of tissues and organs, regulate the proliferation and apoptosis of tissue cells<sup>[4]</sup>. This article reviews the function of the Hippo-YAP signaling pathway and its relevance to liver cancer.

### 2. Discovery and structure of Hippo-YAP signaling pathway

The core of the Hippo signal path is mainly composed of Mst1/2, Lats1/2, Mob, WW45, etc. The main effector molecule is YAP (Yes-associated protein). In 1994, Sudol<sup>[5]</sup> reported for the first time the YAP protein, which consists mainly of the transcriptional enhancer associated domain (TEAD) and the WW domain, and also contains an amino-terminal proline-rich domain. SH3 binding motif, 14-3-3 binding site, CC domain, transcriptional activation region, and carboxy-terminal PDZ binding motif<sup>[6]</sup>. McDonald et al<sup>[7]</sup> found that the carboxy terminus of YAP has no DNA-binding domain but a transcriptional activation domain, which can bind to transcription factors (such as Erb B4, p73, etc.) and exert transcriptional co-activation.

### 3. Regulation of the Hippo pathway

When the upstream signaling molecule activates MST1/2, Mst1/2 phosphorylates Lats1/2 and Mob, which enhances the ability of Mob to bind and activate Lats1/2, then activates Lats1/2 phosphorylation of YAP/TAZ by enhancing YAP The interaction with the 14-3-3 protein causes

YAP to remain in the cytoplasm<sup>[8]</sup> and is degraded, ultimately acting to inhibit cell proliferation. Conversely, when the Hippo-YAP pathway is not activated or blocked, YAP is activated, and unphosphorylated YAP is translocated into the nucleus, binding to TEAD and inducing gene expression involved in cell proliferation, survival, and migration<sup>[9]</sup>.

#### **4. The role of Hippo-YAP signaling pathway in liver cancer**

##### **4.1 Effects on the growth and size of tissues and organs**

YAP has a certain amount of expression in a variety of normal human tissues. Overexpression promotes the growth of normal tissues, causing an increase in tissue and organs, and even canceration. Conversely, YAP inactivation can cause aging and shrinkage of tissues and organs<sup>[10]</sup>. The Hippo signal pathway collects a large number of upstream transcribed signals, conducts a phosphorylation cascade, prevents YAP from entering the nucleus, and forms a signal that inhibits cell growth and development, thereby tightly controlled the number of cells and the size of tissues and organs. Several studies have shown that up-regulation of YAP after Hippo-YAP signaling pathway is blocked can promote the progression of liver cancer. In mouse experiments, high expression of YAP in the liver can lead to liver enlargement, which ultimately leads to the formation of liver cancer in mice<sup>[11]</sup>. Another study overexpressed YAP in the liver of mice. After 1 week, the liver volume increased by 1 time. After 2 weeks, it reached 20% of the body weight of the mice. After 5 months, almost all of the liver cells developed into liver cancer. When the expression level of YAP was restored. After the hepatomegaly can be reduced, the liver parenchyma structure slowly returns to normal<sup>[12]</sup>.

##### **4.2 Effects on cell proliferation and apoptosis**

YAP promotes cell proliferation, inhibits apoptosis, leads to loss of inhibition of cell-to-cell contact and induces malignant transformation of cells, and can cause hyper proliferation and carcinogenesis of hepatocytes in mice overexpressing transgenic YAP<sup>[13]</sup>.

In mammals, cascades in the Hippo signaling pathway negatively regulate the level of YAP through phosphorylation. When certain regulators in the Hippo pathway are mutated or deleted, the activity of downstream YAP is enhanced, which in turn induces some cell growth. Proteins, such as cyclin E and Drosophila inhibitor of apoptosis 1 (DIAP1), increase expression, promote cell proliferation and invasion, and inhibit apoptosis<sup>[14]</sup>.

##### **4.3 Effects on cell migration and invasion**

Xu et al<sup>[15]</sup> confirmed by in vitro cell culture transplantation experiments that hepatoma stem cells extracted from mouse embryos were inoculated into experimental mice to induce the occurrence of liver cancer. The expression of YAP gene in tumor cells was significantly increased. These studies indicate that the level of YAP gene expression in the Hippo signaling pathway is closely related to liver cancer formation.

#### **5. Significance of YAP in the diagnosis, treatment and prognosis of liver cancer**

As mentioned above, YAP as a carcinogen plays an important role in the development of liver cancer, and is associated with tumor graded and typing, so YAP may be a new target for the diagnosis of liver malignancies. YAP overexpression is an early process of human liver cancer formation, and targeted drugs against YAP may become a new treatment, especially the development of multi-targeted drugs containing YAP may achieve good results<sup>[16]</sup>. Studies have found that the most direct way to reduce YAP protein expression is to reduce YAP protein levels at the protein level<sup>[17]</sup>. In addition, YAP must exert its oncogene activity and must interact with downstream regulatory factors, and the Notch signaling pathway can promote the abnormal proliferation of liver cancer. Therefore, inhibitors against Notch signaling pathway are also potential therapeutic methods.

## 6. Conclusion

At present, the main methods for treating liver cancer include surgical resection, radiation therapy and chemotherapy, as well as several methods of combination therapy. However, liver cancer has strong invasiveness and high recurrence rate. Therefore, it is extremely important to improve the early diagnosis rate of liver cancer patients. In recent years, tumor therapy targeting Hippo-YAP signaling pathway has become a research hotspot. The important component of Hippo signaling pathway, YAP, is highly expressed as an oncogene in liver tumors, and it is also an important regulation to promote the formation, development and metastasis of liver cancer. Factors may become a new target for the treatment of liver cancer.

In summary, Hippo-YAP signaling pathway and its downstream target protein YAP plays an important role in the occurrence and development of liver cancer. YAP has a significant correlation with the diagnosis, treatment and prognosis of human liver cancer. By exploring the relationship between Hippo-YAP signaling pathway and liver tumors, it provides a new perspective for further study of the mechanism, diagnosis and treatment of liver cancer.

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## References

- [1] Ming Y L and Zhang W 2018 Research progress on the correlation between Hippo pathway and tumor *Chinese Journal of Obstetrics and Gynecology* **19** 474-475.
- [2] Wang X K and Cai J Q 2017 Progress in Hippo-YAP Signaling Pathway and Its Relationship with Liver Cancer *Cancer Progress* **15** 1396-1399+1476.
- [3] Shi M J, Shao S J and Li J M 2014 Progress in the correlation between Hippo pathway and tumor *Chinese Journal of Cell*. **36** 361-365.
- [4] Zhang N, Bai H and David K K 2010 The Merlin/NF2 tumor suppressor functions through the YAP on-coprotein to regulate tissue homeostasis in mammals *Dev Cell* **19** 27-38.
- [5] Sudol M 1994 Yes-associated protein (YAP65) is a proline-rich phosphoprotein that binds to the SH3 domain of the Yes pro-to-oncogene product *Oncogene* **9** 2145-2152.
- [6] Guo L and Teng L 2015 YAP/TAZ for cancer therapy: opportunities and challenges (review) *Int J Oncol* **46** 1444-1452.
- [7] Donald C B, Intosh S K and Mikles D C 2011 Biophysical analysis of binding of WW domains of the YAP2 transcriptional regulator to PPXY motifs within WBP1 and WBP2 adaptors *Biochemistry* **50** 9616-9627.
- [8] Marta G, Valenti G and Alexander H. 2014 The Hippo pathway in disease and therapy: cancer and beyond *Clinical and Translational Medicine* **3** 1-12.
- [9] Heidary A E, Song K M and Song S Y 2014 Arhgef7 promotes activation of the Hippo pathway core kinase Lats. *The EMBO journal* **33** 2997-3011.
- [10] Camargo F D, Gokhale S and Johnnidis J B 2007 YAP1 increases organ size and expands undifferentiated progenitor cells *Curr Biol* **17** 2054-2060.
- [11] Dong J, Feldmann G and Huang J 2007 Elucidation of a universal size-control mechanism in Drosophila and mammals *Cell* **130** 1120-1133.

- [12]Yin F, Yu J and Zheng Y 2013 Spatial organization of Hippo signaling at the plasma membrane mediated by the tumor suppressor Merlin/NF2 *Cell* **154** 1342-1355.
- [13]Nguyen Q, Anders R A and Alpini G 2015 Yes-associated pro-teiin in the liver: regulation of hepatic development, repair,cell fate determination and tumorigenesis *Dig Liver Dis* **47** 826-835.
- [14]Zhang J, Ji J Y and Yu M 2009 YAP- dependent induction of amphiregulin identifies a non-cell-autonomous component of the Hippo pathway *Nat Cell Biol* **11** 1444-1450.
- [15]Xu M Z, Chan S W and Liu A M 2011 AXL receptor kinase is a mediator of YAP-dependent oncogenic functions in hepatocellular carcinoma *Oncogene* **30** 1229-1240.
- [16]Liu A M, Poon R T and Luk J M. 2010 Micro RNA-375 targets Hippo-signaling effector YAP in liver cancer and inhibits tumor properties[J]. *Biochem Biophys Res Commun* **394** 623-627.
- [17]Pfeifer G P 2016 Properly dividing with YAP *Sci Signal* **9** 3.