Hippo signaling pathway

Hippo signaling pathway, also known as the Salvador/Warts/Hippo (SWH) pathway, controls organ size in animals through the regulation of cell proliferation and apoptosis. The pathway takes its name from one of its key signaling components—the protein kinase Hippo (Hpo). Mutations in this gene lead to tissue overgrowth, or a “hippopotamus”-like phenotype.

The Hippo signaling pathway is a highly conserved signaling pathway that plays a crucial role in the regulation of cell proliferation, organ size, and tissue homeostasis. It was initially discovered in fruit flies (Drosophila) and later found to have similar components and functions in mammals, including humans.

The core components of the Hippo pathway include a series of kinases and transcriptional co-activators that interact with each other to control downstream gene expression. The key regulators of the pathway are the kinases called the Hippo/MST1/2 (mammalian Ste20-like kinases 1 and 2) and LATS1/2 (large tumor suppressor kinases 1 and 2).

When the Hippo pathway is active, the MST1/2 kinases phosphorylate and activate the LATS1/2 kinases. The activated LATS1/2 kinases, in turn, phosphorylate and inhibit a transcriptional co-activator called YAP (Yes-associated protein) and its paralog TAZ (transcriptional co-activator with PDZ-binding motif). YAP and TAZ are key downstream effectors of the Hippo pathway.

Phosphorylation of YAP/TAZ leads to their sequestration in the cytoplasm and prevents their translocation into the nucleus. As a result, YAP/TAZ cannot interact with transcription factors in the nucleus to promote gene expression related to cell proliferation and survival.

On the other hand, when the Hippo pathway is suppressed, the LATS1/2 kinases are inactive, allowing YAP/TAZ to accumulate in the nucleus. In the nucleus, YAP/TAZ interact with transcription factors, such as TEAD (TEA domain transcription factors), to activate target genes involved in cell growth, survival, and tissue development.

The Hippo pathway is tightly regulated and responds to various upstream signals, including cell-cell contact, mechanical forces, and extracellular signaling molecules. These signals are sensed by specialized proteins, such as the cell polarity proteins, Merlin, and the angiomotin family members, which act upstream of the core Hippo kinases to regulate their activity.

The Hippo pathway is critical for controlling organ size during development and maintaining tissue homeostasis in adults. Dysregulation of the pathway has been implicated in various diseases, including cancer. In some tumors, the Hippo pathway is disrupted, resulting in increased activity of YAP/TAZ and uncontrolled cell growth. Thus, understanding the Hippo pathway and its regulation provides insights into the mechanisms underlying tissue growth, regeneration, and disease progression.

A fundamental question in developmental biology is how an organ knows to stop growing after reaching a particular size. Organ growth relies on several processes occurring at the cellular level, including cell division and programmed cell death (or apoptosis). The Hippo signaling pathway is

involved in restraining cell proliferation and promoting apoptosis. As many cancers are marked by unchecked cell division, this signaling pathway has become increasingly significant in the study of human cancer.

The Hippo signaling pathway appears to be highly conserved. While most of the Hippo pathway components were identified in the fruit fly (Drosophila melanogaster) using mosaic genetic screens, orthologs to these components (genes that function analogously in different species) have subsequently been found in mammals. Thus, the delineation of the pathway in Drosophila has helped to identify many genes that function as oncogenes or tumor suppressors in mammals.

Results showed the overexpression of YAP1 and Survivin as well as a decreased activity of large tumor suppressor 1 (LATS1) in high-grade glioblastoma versus anaplastic astrocytoma and low-grade glioma. Furthermore, Aguennouz et al. also demonstrated that miR-221 and miR-10b are specifically involved in Hippo signaling pathway via LATS1 regulation and that their knockdown significantly decreased glioma cell proliferation. This preliminary data confirmed the crucial role of the Hippo signaling pathway in cancer and suggested that miR 221 and miR 10b could be potential therapeutic targets for glioma treatment [1)].

Increasing studies have revealed that metabolic disorders, especially diabetes, are high risk factors for the development of Alzheimer's disease (AD) and other neurodegenerative diseases. It has been reported that patients with diabetes are prone to suffer from cognitive dysfunction (CD). Although abnormal glucose metabolism and deposition of amyloid β (Aβ) are proven to have a closely relationship with diabetes-induced CD, its exact mechanism is still undetermined. In this study, a total of 14 mice were intraperitoneally injected with streptozotocin for 5 consecutive days to mimic diabetic models, and then hierarchical cluster analysis was adopted to classify the diabetic mice into CD and Non-CD phenotypes by the results of Morris water maze test (MWMT). Furthermore, we detected Hippo signaling including mammalian sterile 20-like protein kinases1 (MST1), large tumor suppressors 1 (LATS1), Yes-associated protein (YAP) and phosphorylation of YAP (p-YAP) in brain and peripheral tissues. As compared with control mice, the levels of MST1, LATS1 and p-YAP/YAP ratio were increased in medial prefrontal cortex (mPFC), striatum and hippocampus of CD mice, while these proteins were decreased in gut tissue of CD mice. Additionally, there were significant positive correlations between escape latency and p-YAP/YAP ratio in mPFC, anterior cingulate cortex (ACC) and hippocampus, as well as the level of LATS1 in liver, kidney and gut tissues. In conclusion, alterations in Hippo signaling may contribute to CD induced by diabetes. Therefore, therapeutic interventions improving Hippo signaling might be beneficial to the treatment of diabetes-induced CD and other neurodegenerative diseases [2)].

The Hippo signaling pathway is functionally conserved in Drosophila melanogaster and mammals, and its proposed function is to control tissue homeostasis by regulating cell proliferation and apoptosis. The core components are composed of a kinase cascade that culminates with the phosphorylation and inhibition of Yes-associated protein 1 (YAP1). Phospho-YAP1 is retained in the cytoplasm. In the absence of Hippo signaling, YAP1 translocates to the nucleus, associates with co-activators TEAD1-4, and functions as a transcriptional factor promoting the expression of key target genes. Components of the Hippo pathway are mutated in human cancers, and deregulation of this pathway plays a role in tumorigenesis. Loss of the NF2 tumor suppressor gene is the most common genetic alteration in

meningiomas, and the NF2 gene product, Merlin, acts upstream of the Hippo pathway. Baia et al. show that primary meningioma tumors have high nuclear expression of YAP1. In meningioma cells, Merlin expression is associated with phosphorylation of YAP1. Using an siRNA transient knockdown of YAP1 in NF2-mutant meningioma cells, they show that suppression of YAP1 impaired cell proliferation and migration. Conversely, YAP1 overexpression led to a strong augment of cell proliferation and anchorage-independent growth and restriction of cisplatin-induced apoptosis. In addition, expression of YAP1 in nontransformed arachnoidal cells led to the development of tumors in nude mice. Together, these findings suggest that in meningiomas, deregulation of the Hippo pathway is largely observed in primary tumors and that YAP1 functions as an oncogene promoting meningioma tumorigenesis [3].

Physiologically, The Hippo signaling largely restricts its two downstream effectors, homologous oncoproteins Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ), to a low level of activity by the MST1-SAV1 complex-induced kinase cascade. However, how the negative regulation induced by MST1-SAV1 complex is disrupted to exhibit constitutive YAP/TAZ activation in cancer remains unclear.

Zhu et al.report that miR-130b directly repressed MST1 and SAV1 expression in human glioblastoma cells. Overexpression of miR-130b induced hyperactivation of the YAP/TAZ and enhanced expression of the Hippo signaling downstream genes CTGF and the pluripotency associated markers, including CD133, SOX2, Nanog, MYC and BMI1, leading to promotion of glioblastoma stem cell phenotype. Conversely, inhibition of miR-130b attenuated these effects. These findings provide a novel mechanism for Hippo signaling inactivation in cancer, indicating not only a potentially pivotal role for miR-130b in the progression of glioblastoma, but also may represent a new therapeutic target [4].

References

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