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The Hippo Network in Cancer: AComprehensive Review of Its Role in Tumor Progression and Therapy

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ABSTRACT

The Hippo network pathway, which is found in many different species, is crucial for regulating various biological functions such as development, cell growth, stem cell activity, tissue repair, balance within the body, and the size of organs. Over the past two decades, research has revealed the intricate regulation of this pathway by a complex network of molecules inside and outside cells. Disrupting the Hippo network can lead to various diseases, including cancer. There is increasing evidence linking abnormal Hippo network to the formation of tumors, the spread of cancer cells, and resistance to treatment. Monitoring this route has become a viable approach for treating cancer. New drugs that target the Hippo network have shown anti-cancer effects in animal studies and offer hope for cancer patients. However, the exact molecular mechanisms responsible for how Hippo network causes cancer are not fully understood. Scientists are now investigating the involvement of the Hippo network in both the growth of cancer and its resistance to therapy.

Keywords: Hippo network pathway, Tumorigenesis, Cancer,Drug resistance,Therapeutic target.

INTRODUCTION

Tumors are a significant global health issue, necessitating more research for improved understanding. Researchers analyse tumors from several perspectives, such as genetic alterations or abnormalities during development [1-3]. Biologist Beatrice Mintz proposed in 1978 that cancers originate from developmental abnormalities in the body [1]. Cancer cells' capacity to proliferate and metastasize resembles the growth process of cells in the developing embryo [4]. This demonstrates a significant correlation among embryonic

development and tumor formation [4]. Processes such as cell proliferation, death, and migration that occur in cancer are similarly crucial in the embryonic development of organs indicating Cancers are somewhat linked to the body's developmental processes [5]. Malfunctions in embryo development-related systems may initiate tumor formation and promote their growth. Pathways such as Wnt, Hedgehog, and Notch play crucial roles in development and exhibit significant similarities across many species [3-5]. These pathways are actively engaged and meticulously regulated throughout development [3-5]. After maturation, they should return to a state of tranquillity to maintain proper organ function. Reactivation of these pathways in a mature organ may result in the formation of malignancies [6-7]. We need a comprehensive understanding of this process. The Hippo network plays an essential role in developmental pathway, particularly in regulating organ size. Hippo network often becomes active post-development, unlike other routes. The inactivity of Hippo may result in cell proliferation and migration, processes associated with development and tumorigenesis [6-7]. Hippocrates is often believed to be a mechanism that prevents the formation of cancers in the body [8]. The Hippo network core comprises many proteins that collaborate. When Hippo is activated, it modulates the activity of other proteins, such as YAP/TAZ, hence inhibiting their tumorigenic potential [9]. When Hippo is inactive, YAP/TAZ may translocate into a cell's nuclei and promote tumorigenesis. In liver cancer individuals, decreased Hippo activity is associated with a reduced likelihood of recovery [10-11]. When Hippo is inactive, it may initiate and exacerbate liver cancer in experimental and cell research. The Hippo network regulates several cellular processes and interacts with multiple components inside the cell, complicating the comprehension of its involvement in cancer. The activity of the Hippo network is controlled by various factors, such as how cells physically touch each other (cell-cell contact) and the overall conditions in the surrounding environment. An overabundance of YAP protein in the embryonic brain disrupts the delicate balance between creating new nerve cells (neurogenesis) and the growth of immature ones (progenitor cells). This imbalance is caused by YAP accelerating the cell cycle in progenitor cells. Given Hippo's association with malignancies, developing strategies to inhibit them may provide a promising approach to cancer treatment. Verteporfin is a medication that may target components of the Hippo network and is used in the treatment of eye cancer. The present paper will discuss the mechanism of the Hippo network pathway in tumors, with a particular emphasis on pharmaceuticals that target Hippo, in order to propose novel approaches for cancer therapy [12].

REVIEW

The search was conducted systematically across PubMed, Embase, Web of Science, and the Cochrane Library to find articles related to the Hippo signalling pathways.

Description of critical components and regulators of the pathway

Furthermore, the pathway known as Hippo is a highly conserved signalling circuit that controls several physiological and development-related activities [13]. A great deal of importance goes into making this: Some proteins that play a role in transcriptional regulation include A multitude of proteins collaborate to regulate genes that impact movement and spread of cells, cell death, and the nourishment of stem cells. The proteins in question include MST1/2, SAV1, MOB1A/B, LATS1/2, YAP, TAZ, and the TEAD group [14]. Hormone inputs that operate via G-protein-coupled in the body mechanical motion indications and the metabolic status of cells are among the many signals that regulate the process known as Hippo [15]. Also contributing to this control are aspects of the cell's inherent devices, including the cytoskeleton made of actin, the polarity of cells, and cell-cell interaction. Improper regulation of the pathway known as Hippo has the potential to cause a wide range

of conditions and diseases, including cancer, ocular illnesses, heart conditions, lung conditions, renal issues, hepatic diseases, and immune system disorders [14].

The Hippo network is a key player in maintaining balance within the body

Both the management of organ formation and the preservation of tissue homeostasis are vitally dependent on the Hippocampus network, which is a vital component. The following is a list of some of its most essential features: In addition to the homeostatic remainder of tissues, the control of organ size is also essential. In mammals, the Hippo network acts as a brake on organ growth. It achieves this by modifying (phosphorylating) YAP and TAZ, proteins that normally stimulate cell growth [16]. In addition to this, it regulates the process of cell proliferation, the mechanism of death, and the stemless of cells with respect to a wide range of signals that are both external and intracellular [17]. One of the functions of the Hippo network is to participate in stem cell biology, which is essential for the maintenance of balance in tissues [18]. In order for the Hippo network to function correctly, certain responsibilities are required. As part of the process of tissue restoration, the participant mustbecause YAP is the principal effector of the Hippo network, there is a transient rise in the synthesis of YAP whenever there is injury to the tissue. This not only makes the method of renewing tissue more efficient, but it also increases the formation of progenitor cells that remain continuously present in the tissue all through time. The Hippo circuit is now being studied for the goal of developing individualized regenerative drugs. This is due to the fact that it plays a significant role in preserving the balance of tissues and regeneration [18].

Controlling the growth of organs is one of the more renowned activities of the Hippo network, which is also one of its most important ones. Some alterations occur in genes like Hpo and Wts, in addition to other controllers like Ex, Mer, Kibra, and Ft, which are accountable for the abnormal development of organs in fruit flies. The development of eyes, wings, and other elements are among the modifications that occur throughout this process. Similarly, the same sort of effect happens when the gene Yki is intentionally created in a fly. This is equivalent to what happened in the past. The fact that Yki plays a role for stimulating the growth of cells and tissue preservation is the primary explanation for this particular increase in organ size. After conducting a number of studies on mice, researchers have discovered that the system known as Hippo is also accountable for regulating the dimension of organs in mammals. As an example, whenever the gene Yap is only expressed in the liver of mice, the dimension of the mice's livers increases significantly. This is a result of this gene's unique production. An intriguing feature is that when the overproduction of Yap is stopped, the liver goes through a process that is known as dying, causing it to return to its typical dimensions. This allows the liver to return to its capacity.Furthermore, the omission of genes that are precisely situated in the liver, such as Mst1/2, Sav1, or Nf2, could result in the growth of the individual's liver. It is possible to make the heart enlarged in mice embryos by deleting genes such as Sav1, Mst1/2, or Lats1/2. Furthermore, the alteration of the Yap gene has the potential to affect the growth of cardiac cells as well as their eventual death [17].

It is important to note that not all organs react in the same manner to alterations in the Hippo system. By way of illustration, the deletion of Mst1/2 results in a significant increase in the size of the liver, heart, stomach, and spleen, but it does not affect the kidneys, lungs, or limbs. The fact that this is the case shows that the deletion of Mst1/2 does not affect the other controllers of YAP/TAZ that are present in these organs. In the breast and the gut, eliminating the Yap gene, particularly in those tissues, does not have any effect on the shape or size of those tissues. Even while the deletion of Yap in the mouse liver results in abnormalities in the bile ducts; it does not result in a reduction in the total size of the liver. This may be due to the fact that deletion of Yap allows another gene known as TAZ to become more active. There is a possibility that the pathway known as Hippo or the function of YAP/TAZ does not play a substantial role in the regulation of growth in some organs.On

the other hand, the distinctive impacts of the Hippo process affecting organ growth imply that various organs may utilize distinct techniques to regulate their size. For example, raising the amount of particular cells or precursor cells might be one of the techniques that organs employ to manage their size. There still needs to be complete comprehension of the signals that govern the pathway of the Hippocampus and play a significant role in defining the size of the organ. The modifications in mechanical strain or tension that occur when organs expand might play an essential part in the inhibition of YAP/TAZ when an organ achieves its finished size. The Hippo pathway might use special signalling molecules made by the organs themselves to keep track of their size. We need more research to understand how the Hippo pathway picks up on these signals to control organ growth [17].

Hippo network dysregulation on tumor initiation, progression, and metastasis

Both invasion and metastasis of the tumor are processes that take place when cancerous cells travel from the primary location of the tumor to other areas of the body via the lymphatic or circulatory systems. There is a connection between this activity and a cellular process known as epithelial-mesenchymal transition (EMT), which is an essential step in the development of cancer. EMT plays a significant role in the growth of embryos, the repair of tissues, and the healing of wounds. The EMT, on the other hand, may encourage tumor growth and metastasis in cancer patients. Throughout the process of epithelial-mesenchymal transition (EMT), cells in the epithelial layer undergo a transformation in which they are increasingly similar to mesenchymal cells in shape.

Cells involved in this process switch gears. They lose proteins like E-cadherin that help them stick together (epithelial markers) and gain proteins like vimentin and N-cadherin that make them more mobile (mesenchymal markers). This transition is characterized by these two changes. Mesenchymal tissue cells contain a protein called vimentin, whereas non-neuronal cells generally produce N-cadherin at low levels. Vimentin plays a role in adhesion between cells, while N-cadherin typically circulates at low levels. On the other hand, epithelial cells are the primary locations where E-cadherin is prevalent. A marker of epithelial-mesenchymal transition (EMT) in cancer cells is the overexpression of N-cadherin and a decrease of E-cadherin. Furthermore, MMPs, or matrix metalloproteinase, contribute to the invasion of tumors by degrading the matrix of cells (ECM) and activating extracellular matrix metalloproteinase (EMT). MMPs are a collection of enzymes that breakdown numerous elements of the extracellular matrix (ECM), which makes it easier for tumor cells to move around and invade. A process called EMT allows tumor cells to become more mobile and invasive, contributing to tumor growth and metastasis. MMPs, another group of molecules, help break down surrounding tissue, further aiding the spread of cancer [Fig. 1] [19].

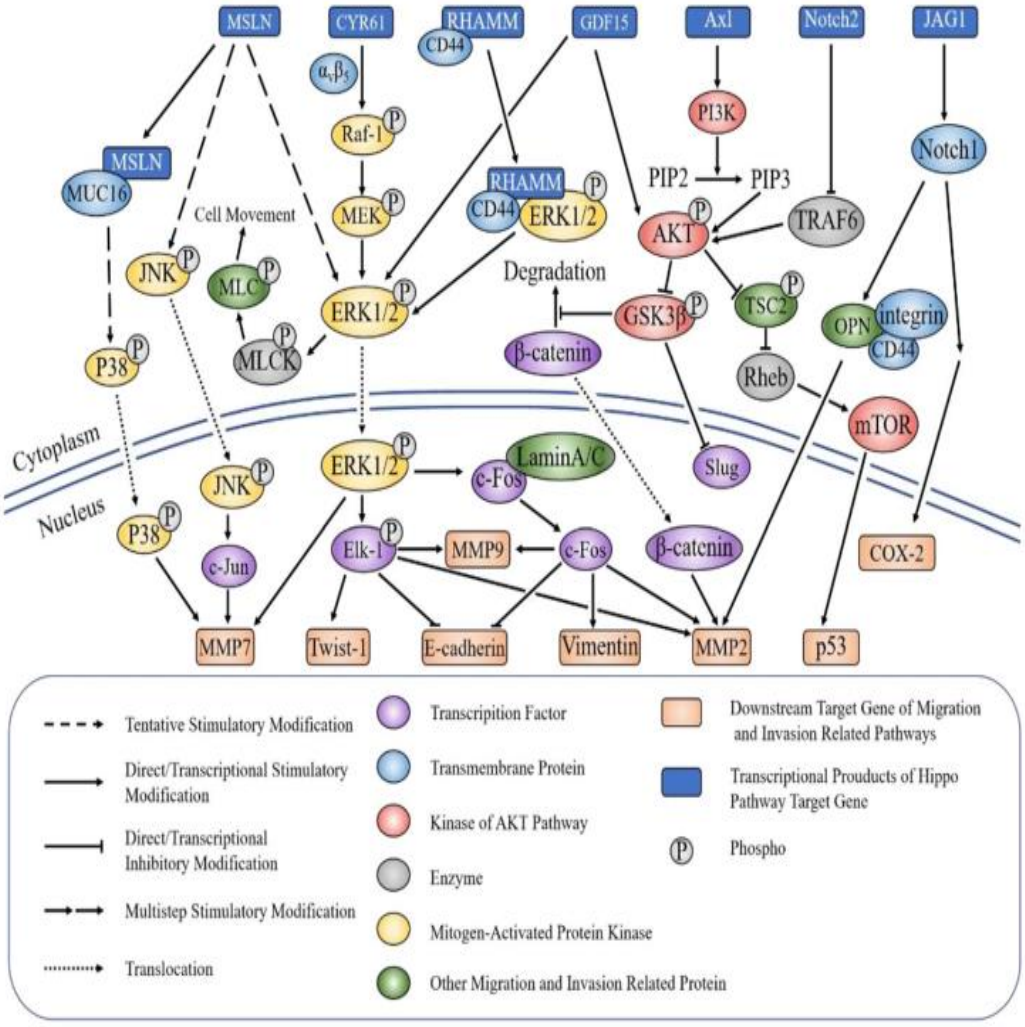

Figure 1: Overall signalling pathways related to the migration in Hippo network

Oncogenic functions of YAP and TAZ in promoting cancer [19]

YAP/TAZ are primarily controlled by mechanotransduction, a process in which cells interact with their environment by exchanging forces that are physical, such as with the ECM or extracellular matrix [20-21]. Cells use mechanical messages to detect modifications to their surroundings as well as their own structure, orientation, and cytoskeletal arrangement. Mechanical forces in tissues are generated by the arrangement of cells within the 3D tissue framework and the stroma milieu. Cells produce forces that communicate with the extracellular matrix (ECM) via binding to integrins, linking to the F-actin cytoskeleton via Focal Adhesions, which include proteins such as ILK, FAK, and Src [22-24]. Cells respond to external stimuli by enhancing the ability to contract of F-actin and restructuring their cytoskeleton via the involvement of proteins such as Rho or Rac1, myosin, and ROCK [25]. The Integrin/FA/Rho-Rac/ROCK/F-actin signalling system is an intriguing target for therapeutics, as will be explored later. An important topic is the connection between the F-actin framework of cells that are stimulated and the migration of YAP/TAZ into the nucleus for stimulation [25-26]. YAP/TAZ translocate into the nucleus as nuclear pores expand as a result of nucleo-cytoskeletal interaction. Mechanosignalling enhances the reaction times of YAP/TAZ by dissociating them from SWI/SNF intricate elements [27]. In the absence of LATS1/2, cells do not exhibit altered responses to mechanical stimulation [20, 25–30]. It is uncertain how F-actin in the body's cytoplasm regulates the nuclear entrance of YAP/TAZ, such as by potentially trapping or degrading molecules that inhibit their nuclear translocation.

Research indicates that LATS1/2 may play a role in the interaction between F-actin and YAP/TAZ. If LATS1/2 were affected by F-actin, their function would be altered in response to biomechanical inputs [31]. However, there is little evidence to support this. LATS1/2 may serve as a regulatory mechanism that is not essential for the F-actin/YAP/TAZ pathway but is capable of suppressing it. LATS kinases may influence the organization of F-actin via acting on ENA and AMOT, potentially impacting the activity of YAP/TAZ. YAP phosphorylated at LATS1/2 sites changes in response to alterations in mechanical signals [32]. Nevertheless, LATS1/2 may not directly influence the reaction of YAP/TAZ to mechanical signals since the phosphorylation might be a consequence of YAP/TAZ being prevented from accessing the nucleus, where LATS1/2 primarily functions. Knowing the connection between mechanosignalling and YAP/TAZ remains a mystery. Although Hippo network deactivation may not be the primary cause of excessive YAP/TAZ activity in tumors, investigating the function of mechanosignalling in this procedure is important. Regular tissue organization may inhibit tumor growth by impeding the accumulation of YAP/TAZ in the cell nucleus [26] [30] [33]. Trauma and renewal may trigger YAP/TAZ activation via biomechanical alterations. However, in tissues that are healthy, the stimulation is transient and ceases after the tissue has healed, leading to the deactivation of YAP/TAZ. Tumors resemble permanent injuries, displaying altered components that do not heal, resulting in continuous YAP/TAZ activity caused by environmental alterations [21][30][33][34-37].

Table 1: Identifies the different proteins in Hippo network pathway [38-39]

Protein	Function	Pathological Implications
MST1/2	Phosphorylate LATS1/2	Reduced MST1/2 activity linked to cancer progression
LATS1/2	Phosphorylate YAP/TAZ	Loss of LATS1/2 activity associated with tumour growth
YAP/TAZ	Transcriptional co-activators	Overexpression linked to tumor growth and metastasis
TEAD	Transcription factors	Overactivation associated with tumor progression
NF2 (Merlin)	Regulates Hippo network at the membrane	Mutations in NF2 lead to tumor formation (neurofibromatosis type II)
AMOT	Angiomotin, regulates YAP localization	Dysregulation contributes to angiogenesis and tumor growth

Preclinical and clinical studies investigating the efficacy of Hippo network inhibitors in cancer treatment

Wu and co-workers identified MGH–CP1 as a drug that inhibits autopalmitoylation in TEAD. They verified this by examining the binding of MGH-CP1 to TEAD. They synthesized two novel substances, CP-58 and CP-55, by amalgamating components of MGH–CP1 with flufenamic acid. CP-55 shown significant efficacy in inhibiting cell proliferation in research studies. Basilea Pharmaceutica, a Swiss business, discovered a set of molecules like flufenamic acid that has the ability to inhibit TEAD. One of these chemicals successfully halted tumor development in mice. Genentech researchers discovered a chemical, GNE-9886, which converts TEAD into a protein that halts the proliferation of cancer cells. Additional drugs with similar mechanisms of action were discovered to be efficacious against cancer cells. Ikena Oncology created two chemicals that inhibit TEAD, with one being particularly effective against certain cancer cell types. Hong and Probatti et al. identified a chemical that enhances TEAD activity, potentially beneficial for wound healing. Vivace Therapeutics developed two medicines that inhibit TEAD function, with one specifically targeting malignant mesothelioma. Astra Zeneca created a chemical that might enhance TEAD activity in heart cells, potentially promoting heart cell development. Another chemical, 53, was responsible for the anti-cancer cell activity by inhibiting the YAP1 and TEAD protein interactions. The findings have the potential to address disorders associated with the Hippo signalling system, including cancer [40].

The involvement of Hippo network in the regulation of cancer stem cells

The differentiation of cells in mammals begins during prior to implantation in the very beginning stages of life. Currently, some cells differentiate into a protective outer layer known as the trophectoderm (TE), whereas other cells differentiate into the inner cell mass (ICM). A layer of cells called the trophoblastic epithelium (TE) is essential for an embryo to implant in the womb. These cells also contribute to the development of the placenta, which nourishes the growing baby. Additionally, there are special cells called embryonic stem cells (ESCs) found within (ICM) cellular mass present on the inner side of early embryos. These cells possess self-renewal capabilities and the capacity to differentiate into many cell types and tissues, which makes them very favourable for use in the field of regenerative therapy. Researchers have identified a link to the Hippo network system and the properties of stem cells. Embryos that lack the protein YAP fail to grow correctly and have abnormalities in the blood vessels of the yolk sac. TEAD4, a protein controlled by YAP, is essential in deciding the destiny of cells in the first embryo. TEAD4 facilitates the expression of genes crucial for TE formation, such as Cdx2 and Gata3. When YAP ends up inside the cell, cell-to-cell connections and certain proteins in the Hippo network control YAP's location. Additional proteins within the Hippo network, including NF2 and AMOT, are involved in controlling YAP and impacting cell destiny in the first stages of growth. TAZ is found in developing embryos. However, its absence does not have as profound an effect on growth as YAP. The results emphasize the significance of YAP and TEADs in influencing cell destiny in the first stages of embryonic growth [41].

The Hippo network is now acknowledged as a key regulator of pluripotency in conditions in laboratories. Previously, BMP and LIF signals maintained mouse embryonic stem cells in an undifferentiated, regenerative state, but human ESCs need signalling from FGF, BMP, and TGF-β/activin. It is crucial to balance these signals precisely to prevent ESCs from differentiating into other cell types. YAP and TEADs are thought to be involved in preserving pluripotency due to their high expression in embryonic stem cells, neural stem cells, and hematopoietic stem cells. Research has shown that YAP and TEAD2 have the ability to activate the genes Oct4 and Nanog, both of which are essential for preserving the pluripotent state of embryonic stem cells (ESCs). When YAP and TEAD2 are limited or inhibited, embryonic stem cells have a tendency to differentiate into endoderm cells. YAP's involvement in maintaining pluripotency is also observable in induced pluripotent stem cells (iPSCs). Studies have shown that YAP gets activated during the conversion of human fibroblast cells into iPSCs. Introducing YAP into the components used for cell reprogramming enhances the effectiveness of iPSC production, demonstrating YAP's beneficial influence on preserving stem cell characteristics. The Hippo network could communicate with other networks to support the preservation of pluripotency. TAZ may interact with Smad2/3 to support the nuclear retention of Smad complicated systems, leading to the upregulation of pluripotency markers. YAP interacts with Smad1 to control the proliferation of genes crucial for preserving ESCs during BMP stimulation. YAP, TAZ, and TEAD proteins are essential for preserving the pluripotent characteristics of both embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). They assist in fostering stem cell characteristics and regular cell growth, and they play a role in controlling the activation of genes that are essential for preserving pluripotency. This demonstrates the intimate association between the Hippo system and networks regulating cell fate and pluripotency, underscoring its significance for growth and stem cell physiology [41].

Table 2: Summary of hippo pathway and its implications

Proposed Work	Finding	Reference

Critical components and regulators of the Hippo network	A malfunctioning Hippo network disrupts the normal functioning of cells, potentially leading to a range of diseases including cancer and issues with vital organs like the heart, lungs, kidneys, liver, and the immune system.	J. K. Holden and J. J. Crawford [13]
The Hippo network plays an essential role in ensuring that organs develop to an appropriate size. It prevents organs from becoming too large or too small, which could impair their function.	The Hippo network acts like a master switch, regulating organ growth by dictating which cells live and which die. It also safeguards stem cells, ensuring a healthy reserve for tissue renewal. This pathway is essential for maintaining balanced tissue and proper organ formation throughout the body.	B. Zhao, K. Tumaneng, and K.-L. Guan [16] F.-X. Yu, B. Zhao, and K.-L. Guan [17] Y. Wang, A. Yu, and F.-X. Yu, [18]
Hippo network dysregulation in tumor initiation, progression, and metastasis	Disruptions in the Hippo network can create a perfect storm for cancer. Tumors grow more aggressively, become more adept at spreading, and the cancer cells themselves develop properties that allow them to travel more readily.	H.-L. Li [19]
Oncogenic functions of YAP and TAZ in promoting cancer	Proteins called YAP/TAZ play a critical role in tumor development. When their levels rise in cells, the risk of cancer growth and spread increases. This process appears to be heavily influenced by how cells perceive and respond to physical forces in their environment.	S. Dupont [20] T. Panciera, L. Azzolin, M. Cordenonsi, and S. Piccolo[21]
Preclinical and clinical studies on Hippo network inhibitors in cancer treatment	Scientists are developing medications that target specific components of the Hippo network. These drugs hold potential for controlling cancer by slowing down the growth of cancer cells and hindering tumor progression.	E. Barry, Vladimir Simov, I. Valtingojer, and O. Venier [40]
Role of Hippo communication network in cancer stem cells	This pathway acts like a switch for stem cells, regulating their properties and directing their transformation into specific cell types needed for healthy tissues. This is essential for maintaining tissue health and promoting healing after injury.	J. Mo, H. W. Park, and K. Guan[41]
Exploring the mechanisms of Hippo network in the renewal of the liver may pave the way for novel therapies targeting liver disorders.	Disruptions in the Hippo network can lead to abnormal liver function, characterized by excessive growth (hepatomegaly) and accelerated stem cell proliferation. These changes can ultimately contribute to the development of liver tumors.	J. Mo, H. W. Park, and K. Guan[41]
Hippo communication network role in skin development and diseases	The Hippo network acts like a guardrail, keeping skin growth in check. When it malfunctions, the skin can thicken excessively (epithelial thickening), creating conditions favorable for skin cancer development.	J. Mo, H. W. Park, and K. Guan[41]
Hippo communication network role in the nervous system	The Hippo network acts like a conductor, orchestrating growth, transformation, and function of brain stem cells, crucial for brain development. When it malfunctions, it has been linked to certain brain tumors.	J. Mo, H. W. Park, and K. Guan[41]
Hippo communication network role in the cardiac system	A healthy Hippo network is crucial for maintaining a healthy heart. It controls how heart muscle cells grow, enlarge, and even participate in healing after injury. Disruptions in this pathway can contribute to various heart problems.	J. Mo, H. W. Park, and K. Guan[41]

CONCLUSION

The Hippo circuit is now recognized as a crucial controller of development and proliferation in both cardiac and muscular tissues. The significance of YAP in heart muscle is especially crucial, since it plays a vital role in encouraging the growth of cardiomyocytes for rejuvenation. The pathway's interaction with other growth-promoting pathways, such as Wnt and IGF signalling, further highlights its significance in cardiac and muscle biology. However, the exact mechanisms and interactions within the Hippo network, especially regarding the contrasting functions of YAP and TAZ, require further investigation. Understanding these pathways could lead to new insights into heart and muscle development and potentially new therapeutic approaches for treating heart disease and muscle disorders.

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