A narrative review for the Hippo-YAP pathway in cancer survival and immunity: the Yin-Yang dynamics

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Abstract: The Hippo-YAP pathway is fast becoming a key instrument in regulating cancers. Binary oppositions, also known as the Yin-Yang dynamics in Chinese, have emerged in its effects. Some oppositions are attributable to in vitro and in vivo experimental conditions, some are due to differences between cancers or species, some are derived from its inherent duality endowed by upstream and downstream signaling, and some are yet unresolved mysteries. However, as bewildering they are, few have been noticed and defined so far. In this review, we first look back on the Hippo pathway which was initially identified more than a decade ago. We then focus on tumor biology, especially some latest popular mechanisms that regulate tumor cell survival, such as ferroptosis, autophagy, and apoptosis. The third chapter is concerned with the findings of the relationship between the Hippo pathway and tumor immunity on the microenvironment in which tumor cells progress. In each of these main sections the contradictory points of the Hippo pathway are elucidated and thoroughly examined. On one hand, the Yin-Yang dynamics of the Hippo pathway brings about considerable challenges for current research; on the other hand, this work will generate fresh insight into it and offer opportunities for subsequent drug development for cancer and regenerative medicine.

Keywords: Hippo pathway; cancer; ferroptosis; autophagy; apoptosis

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Introduction

The Hippo pathway was first described in Drosophila melanogaster as a tumor suppressor (1,2), which could inhibit the cell growth and normalize the organ size (3). Later, it was found that the Hippo pathway was well-conserved in mammals and played the same role as in Drosophila melanogaster, e.g., managing cell behavior, dictating cell differentiation, and maintaining tissue homeostasis. More profoundly, the Hippo pathway perturbation and mutation have been observed in many types of human cancers, including lung cancer, colorectal cancer, breast cancer, and liver cancer, etc. (4,5).

But it is still debatable whether the Hippo pathway gives rise to cancer or acts as a tumor suppressor. The specific mechanisms that regulate the contradicting activity of the pathway are under intensive investigation. In this paper, we will give a brief overview on molecules of the Hippo pathway and summarize the current knowledge on the two faces of the Hippo-YAP pathway on cancer progression. We present the following article in accordance with the Narrative Review reporting checklist (available at https://
The canonical Hippo-YAP pathway members

The Hippo pathway is composed of a large network of proteins with serine/threonine kinase activity (5-7), including neurofibromatosis type 2 (NF2) (homologs of Drosophila Merlin), mammalian STE20-like protein kinase 1 (MST1. also known as STK4), and MST2 (also known as STK3) (homologs of Drosophila Hippo), large tumor suppressor 1 (LATS1), LATS2 (homologs of Drosophila Warts), the adaptor proteins Salvador homologue 1 (SAV1), MOB kinase activator 1 (MOB1), the mitogen-activated protein kinase kinase kinase kinase (MAP4K) and TAO kinases (TAOK) take parts in the cascade. Recruitment of NF2 to the plasma membrane initiates the phosphorylation of MST and LATS, which leads to phosphorylation of YAP and TAZ (8,9).

MST1/2 exist in a complex with SAV1, which phosphorylates and activates the downstream kinase MOB/LATS1/2 complex. In parallel to MST1/2, the mitogen-activated protein kinase kinase kinase kinase (MAP4K) (homologs of Drosophila Hppy) family and TAO kinases (TAOK) perform the same function (10). The activated LATS1/2 phosphorylates YAP/TAZ on five (YAP) and four (TAZ) conserved serine residues (6), leading to its cytoplasmic retention by 14-3-3 and β-TrCP-mediated ubiquitination and proteasomal degradation.

On the other hand, when the Hippo pathway kinase cascade is inactivated, YAP and TAZ are dephosphorylated and translocate into the nucleus where YAP/TAZ regulate genes associated with cell growth, proliferation, survival, and metabolism. Without DNA-binding domain, YAP/TAZ play their roles by interacting with transcription factors, such as ErbB4, Runx2, Smad, TEAD, and p73. The major partner of YAP/TAZ is the TEA domain (TEAD) proteins (homologs of Drosophila Sd). Target genes of YAP and TEAD include connective tissue growth factor (CTGF), integrin-αV (ITGAV), amphiregulin (AREG), etc. In the absence of nuclear YAP/TAZ, TEADs bind to

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Vg domain-containing transcriptional cofactor-like protein 4 (VGLL4) (homologs of Drosophila Tgi), and thereby inhibit the expression of these target genes (15).

**Hippo-YAP-regulated tumor survival**

**Ferroptosis**

Ferroptosis is a newly discovered and utterly distinctive death form, first observed when RAS-selective lethal small molecule erastin brought about it in cancer cells (16). When later digging into the mechanisms of it, researchers found the eradication process was featured with the accumulation of ROS and mere iron-dependency. Ferroptosis was thus given the name (17). Glutathione peroxidase 4 (GPX4) (18) is a key element in this process. GPX4 is a membrane lipid repair enzyme under normal circumstances, capable of reducing lipid peroxides in a complex cellular membrane environment (19). When it malfunctions, it fails to limit the growth of lipid-based reactive oxygen species (ROS), incurring ferroptosis (20,21). Erastin inactivates GPX4 through glutathione (GSH) depletion (18). Specifically, erastin inhibits system X_c^−, a 1:1 cystine:glutamate exchange antiporter that blocks cystine uptake and reduces glutamate efflux at the same time (22). System X_c^− can thus control GSH synthesis by regulating glutamine and cystine. In clear cell renal cell carcinoma (ccRCC), cancer cells have been identified highly sensitive to the depletion of glutamine and cystine (23). Furthermore, when taking cystine aside, glutamine can still do the solo dance in the death process. It was found that ablating glutaminolysis can protect heart tissue from ischemia-reperfusion injury caused by ferroptosis (24) (Figure 2).

Another in vitro study (25) found that erastin triggered severer cell death in 3D tumor spheroids formed by MDA231 and H1650 cells as the cell density increased, leading to the conclusion that high cell density more rapidly depletes glutamine. Li et al. (26) summarized that glutamine metabolic pathways play a regulatory role in ferroptosis. What makes it more intriguing is that some cancer cells show higher uptake of glutamine than T cells and myeloid cells do (27). This phenomenon contradicts the Warburg effect, which is widely considered significant in tumor cells for adenosine triphosphate (ATP) generation through glycolysis (28). The way they applied ccRCC for measuring the consumption of glucose and glutamine resembles that of Miess et al. (23), who demonstrated that renal cancer cells are highly dependent on the GSH/GPX pathway to stay alive. Therefore, for RCC, glutamine is essential for tumor metabolism. Otherwise, the deficiency of glutamine would not only lead to impaired ATP production but also make cancer cells susceptible to ferroptosis.

Scientists agree that YAP/TAZ increase sensitivity to ferroptosis and that Hippo signaling pathway suppresses ferroptosis. The molecular mechanism behind this relationship has been hunted down to several ferroptosis
modulators, such as ACSL4, TFRC (25,29) and SLC7A11 (30).

Despite these solid findings, the actual anti-tumor effect of YAP-promoting ferroptosis is still debating. Wu et al. (25) demonstrated that except for MDA231 cells, the cell death rate went down as the cell number rose up, because the expression of ACSL4 and TFRC decreased along with the increase of cell density. Yang et al. (31) found that the sensitivity to ferroptosis was influenced by cell density as well, and that low-density but not high-density ovarian cancer cells were highly sensitive to ferroptosis. Similarly, with the confluence of HCT116 cells increasing, increased phosphorylation and decreased nuclear localization of YAP rendered cancer cells resistant to ferroptosis. It is because E-cadherin (ECAD) is required for building intercellular contact in cells (32) and that ECAD is able to activate the intracellular NF2 and Hippo signaling pathway. With the activation of NF2 and Hippo signaling, YAP/TAZ entry into the nucleus is inhibited, preventing the target genes, ACSL4 and TFRC, from playing a role in promoting ferroptosis. Though glutamine deprivation is the trigger for ferroptosis, depleting glutamine yet fails to restore ferroptosis in these confluent cells. The reason is that high-density or high-confluence cells in the tumor setting do not die from ferroptosis while consuming glutamine (Figure 3). Thus, other than YAP-activated tumors, tumors irrelevant to the Hippo pathway perturbation are virtually unaffected by ferroptosis.

When YAP is needed for exerting its repair and regenerative functions at low cell density or confluence, cells are instead sensitive to ferroptosis. Of course we cannot guarantee this since the biological function of ferroptosis still remains unexplained under normal physiological conditions (30).

Except for that new perspective on glutamine metabolism, most past and recent studies have been based on the Warburg effect. Significant implications as the new view may have in imaging, the veracity of previous experiments should not be ignored. Thus, we elucidate the related mechanism from the view of glucose metabolism. First, aerobic glycolysis increases global O-linked beta-N-acetylglucosaminylation (O-GlcNAcylation). As a monosaccharide-based modification, Uridine-diphosphate

**Figure 3** ‘Ferroptosis on’ in low-density/confluence cells, and ‘ferroptosis off’ in high-density/confluence cells. As the number of cancer cells increases, more glutamine will be consumed. However, instead of being more sensitive to ferroptosis, cancer cells develop resistance to ferroptosis. This is due to the inhibition of YAP activation in high-density/confluence cells and reduced expression of ferroptosis genes, such as ACSL4 and TFRC. When there are fewer tumor cells, their metabolism scarcely requires excessive consumption of glutamine. YAP is activated to promote cell proliferation, but, as inferred from the scenario of high cell density/confluence, it also promotes ferroptosis.
N-acetylglucosamine (UDP-GlcNAc) is its only sugar donor, which is synthesized from glucose through the hexosamine biosynthetic pathway (HBP) (33). It has been identified that O-GlcNAcylation at the Ser109 site (34) and Thr241 site (35) of YAP stabilized YAP by antagonizing its Hippo-dependent phosphorylation, which incurred high-glucose-induced liver tumorigenesis. Interaction between YAP and O-GlcNAcylation links glucose abundance to Hippo signaling activity and tumorigenesis (36). Besides, YAP upregulates enzymes in glycolysis (37), including some critical rate-limiting enzymes. A positive loop therefore forms between YAP and glycolysis. Accordingly, as tumor cells consumed glucose, ferroptosis was eventually enhanced as well, proven by an increase in TFR expression elicited by YAP-O-GlcNAcylation (30).

Surprisingly, erastin, Sorafenib and other system $X_c^T$ inhibitors could downregulate YAP at both the mRNA level and the protein level (38). This finding seems contradictory compared to the literature of Wu et al. (25). The authors (38) made a clarification that two theories were complementary to each other because the TEAD-based transcription program stimulated by YAP was a prerequisite for triggering ferroptosis, while the degree of ferroptosis was determined by the remaining YAP levels. They used in vitro study to prove that it was the accumulated endogenous glutamate in the lung adenocarcinoma (LUAD) cell that triggered the suppression of YAP through ADCY10/PKA/GFPT1 signaling axis, in which GFPT1 was the rate-limiting enzyme of HBP. Meanwhile, the data about xenografts generated by H1975 and A549 cells validated that the suppression of YAP induced the inhibition of ferroptosis-associated tumor growth.

Therefore, in the entire process of ferroptosis, YAP is critical for regulating both the initiation and progression of it. Firstly, YAP exerts a tumor-suppressive effect, but later it exerts an oncogenic effect.

**Autophagy**

Autophagy is not only a form of cell death, but also a mechanism of cell survival under stress, e.g., hypoxia, nutrient limitation, and redox stress (39,40). In normal cells and tissues, autophagy resembles quality inspection system, which maintains cellular homeostasis through wiping out damaged organelles and proteins. The process is regulated by more than 30 autophagy-related genes (ATG) (41). After catabolism, degradation products are recycled to the cytoplasm for cellular replenishment. In an in vivo study, conditional (acute) systemic (whole-body) Autophagy deficiency in adult mice resulted in a depletion of dedicated nutrient stores during fasting. Without exogenous nutritional supplementation, this systematic metabolic defect may cause lethal hypoglycemia (42).

Autophagy has the potential to fuel almost all aspects of central carbon metabolism through mediating the degradation of various macromolecular complexes, such as carbohydrates, proteins, DNAs, and lipids. The main catabolic process is carried out by the degradative enzymes from lysosomes in autolysosomes that are formed by the fusion of autophagosomes and lysosomes (43-45).

Even though autophagy has been extensively studied, effects of autophagy on tumor development remain contradictory. For example, there are two conflicting papers published in Nature. One (46) declared that depletion of Atgs impaired metabolism, proliferation, survival and malignancy of spontaneous tumors in autologous cancer models; but the other one (47) introduced the concept of replication crisis and noted that autophagy, if inhibited, could lead to tumors bypassing the replication crisis, which is necessary for the initiation of cancer. Wen et al. (48) confessed that they still did not know whether autophagy promoted or inhibited cancer. Kimmelman et al. (49) also reviewed that autophagy was initially thought to have a tumor-suppressive role, capable of removing damaged or redundant organelles and eliminating ROS. More recently, however, autophagy has been found to have a key tumorigenic role, particularly in promoting tumor metabolism in a variety of cancer types. It has been demonstrated that autophagy could help tumors to cope with low-nutrient conditions and chemotherapy-induced stress (50).

Leaving aside the dual role of autophagy on tumors, the relationship between the Hippo-YAP pathway and autophagy is quite contradictory as well. High mobility group box 1 (HMGB1), a renowned regulator of autophagy (51), can be enhanced by YAP, resulting in glioma progression. In a simulated tumor microenvironment (TME) with high cell density and high cell confluence, YAP/TAZ double knockdown inhibits autophagosome formation, and autophagy promotes the cell proliferation with activated YAP/TAZ.

Conversely, in liver cancer development, impaired autophagy triggers YAP stabilization, while YAP can be degraded by autophagy (52). In colorectal cancer (CRC) (53), YAP-TEAD complex upregulates the transcription of the apoptosis-inhibitory protein Bcl-2,
which subsequently shuns autophagy-related cell death and promotes CRC progression. Furthermore, rapamycin-activated autophagy counteracts YAP to exert its function.

Pavel et al. (54) summarized that autophagy compromise could either activate or inhibit YAP/TAZ in different cell lines. Downregulation of YAP/TAZ upon autophagy suppression was observed in MCF10A, HEK293T, HeLa, and pMECs cells, while upregulation of YAP/TAZ activity was spotted in HepG2 and THLE2 cells. Then it was found that CTNNA1 determined the function of YAP/TAZ-autophagy axis. In cells where autophagy and YAP/TAZ were cooperative, the relative ratio of CTNNA1 basal levels was higher than 0.5, while in cells where autophagy was antagonistic to YAP/TAZ, it was around 0.3 or less. Thus CTNNA1, as one of α-catenin, determines the differential effects of autophagy on YAP/TAZ activity.

**Apoptosis**

Compared to autophagy and ferroptosis, apoptosis is now a less popular or controversial topic when it comes to the relationship with cancers. A fair amount of literature has suggested that apoptosis and the Hippo-YAP pathway were closely linked. By inducing cell-cycle arrest, cellular senescence and apoptosis, the p53 family proteins take a tremendous part in tumor suppression, among which the role of p53 is particularly prominent (55). Other family members include p63 and p73, two homologs of p53 that share homology in DNA sequence, protein structure and functional features (56).

Apoptosis is an essential mechanism to eliminate oncogenesis. p53 earns its title ‘Guardian of the genome’ (57) because of its ability to detect DNA damage, hypoxia, and oncogenic events, and to eliminate them through cell-cycle arrest, senescence, apoptosis (58,59). In fact, over half of human cancers harbors mutant p53 (60).

In an earlier report (61), LATS2 activated p53 in the nucleus and translocation of LATS2 was positively regulated by p53. Then, Aylon et al. (62) came up with an indirect and novel way LATS2 regulated the p53 pathway. Apoptosis—stimulating protein of p53-1 (ASPP1) plays a key role in proapoptotic response. LATS2 phosphorylates ASPP1 and drives its nuclear localization in HCT116 cells, shunting p53 to the proapoptotic promoter. YAP antagonizes the tumor suppression function of the LATS2/ASPP1/p53 axis by disrupting LATS2-ASPP1 binding. Vigneron et al. (63) confirmed it from the opposite side: YAP would remain nuclear and ASPP1 would remain cytoplasmic in cancers with reduced LATS2 activity. Additionally, LATS1/2 can bind to murine double minute2 (MDM2) and inhibit it, which is the first identified inhibitor of p53; hence the stabilization of p53 (61,64,65) (Figure 4A). It seems that LATS1/2 does suppress oncogenesis by promoting p53, while YAP stands against this anti-tumor process.

p63 consists of full-length transactivation domain (TA) isoform, TAp63, and the amino-deleted ΔN isoform. The paradox is that the former structurally and functionally resembles p53, while its counterpart, ANp63, facilitates oncogenesis by indirectly affecting YAP nuclear transposition in head and neck squamous carcinoma (66,67), as evidenced by the overexpression of ΔNp63 and YAP in this kind of cancer (68).

In response to genotoxic stresses, p73 functions similarly to p53 (69,70). Firstly, the non-receptor tyrosine kinase c-Abl (ABL1), activated by stresses, phosphorylates p73 at Tyr99 and initiates the DNA damage-induced apoptosis (71,72). There is also an indirect way to apoptosis. Activated c-Abl can phosphorylate YAP at Tyr557 (73). The modified YAP preferentially associates with p73 in targeting apoptotic gene promoters (74,75) and stabilizes it by preventing nuclear export and subsequent degradation (76). It should be noted that the interaction of p73 with Abl and YAP is an independent event, as binding to c-Abl and tyrosine phosphorylation of p73 are not required for association with YAP (77) (Figure 4B). Nevertheless, such interaction differs from YAP in the p53 pathway: c-Abl-mediated phosphorylation of YAP is proapoptotic (73), and it can be deducted that LATS1/2 is not proapoptotic in the p73 pathway, since LATS1/2 phosphorylates YAP at different sites. Despite the oncogenic and pro-proliferative property of YAP, YAP can be a tumor suppressor (77). Another research (78) also validated the idea. It proved that under DNA damage, the reintroduction of YAP in acute lymphoblastic leukemia (ALL) (Jurkat) or AML (OCI/AML3) reduced cell proliferation and induced apoptosis, while the overexpression of LATS prevented the phosphorylation of p73 and inhibited apoptosis. Still, in the absence of this condition, YAP prefers to interact with the oncogenic transcription modulator RUNX, bringing about increased degradation of p73 (79).

Apart from ABL1-centered apoptosis, RAS association domain family 1A (RASSF1A) elicits apoptosis through the p73 pathway as well (80). A previous study (81) demonstrated that the Raf1 proto-oncogene bound to MST2, preventing its activation and proapoptotic signaling. RASSF1A can abrogate the Raf1-MST2 complex, and downregulation...
of endogenous MST2 in MCF7 decreases RASSF1A-induced apoptosis (80) (Figure 4C). Thus, MST2 may serve as a hub that functionally connects proliferative and proapoptotic pathways. More interestingly, the authors (80) suggested that LATS1 also had a dual role. It is widely acknowledged that LATS1/2 results in the cytoplasmic sequestration and proteasomal degradation of YAP/TAZ, but in response to RASSF1A, it may help YAP bind to p73 and nuclear translocation (80).

There are some more dizzy contradictions. For example, unlike epithelial carcinomas, hematologic malignancies do not appear to require p53 inactivation, but they need the early inactivation of the ABL1-YAP-p73 axis. However, in chronic myeloid leukemia (CML), ABL1 can be tumorigenic since it is also a pro-proliferative factor if its activation goes uncontrollable (82-84); For WT and p53-mutant MM (multiple myeloma) cell lines, MST1 knockdown recovers apoptosis, suggesting that restoring YAP levels could be a new treatment strategy in tumors with p53 inactivation (78); Likewise, a positive feedback loop also exists between YAP and p53: YAP can bind to TP53 gene promoter and upregulate p53 expression, resulting in apoptosis. In turn, p53 can bind to the YAP promoter and upregulate YAP expression as well, forming another positive loop.

Figure 4 The conflicting relationship between the Hippo pathway and apoptosis. (A) LATS1/2 helps p53 bind to the proapoptotic promoter by promoting apoptosis-stimulating protein of p53-1 (ASPP) entry into the nucleus and inhibiting YAP and murine double minute2 (MDM2); at the same time, p53 also actively regulates LATS2, thus forming a positive loop of LATS1/2 and p53. (B) Having received the signal of genotoxic stress, the non-receptor tyrosine kinase c-Abl phosphorylates p73 and YAP at different tyrosine sites, different from the phosphorylation by LATS, the latter being able to stabilize p73 after phosphorylation. Furthermore, c-Abl is a negative regulator of TEADs, which co-activates anti-apoptotic target genes with YAP. (C) The MST2-Raf1 complex prevents MST2 activation. The complex can be abolished and the inactivation can be reversed by RAS association domain family 1A (RASSF1A). When RASSF1A is present, LATS1/2 does not isolate YAP outside the nucleus, but facilitates its entry into the nucleus and binding to p73, thereby transcribing proapoptotic genes. Although YAP is not phosphorylated at tyrosine sites at this point, it exerts a proapoptotic effect. It is LATS1/2 that plays the ‘the Yin-Yang dynamics’ role. (D) Instead of dampening apoptosis by disrupting LATS2-ASPP1 binding, YAP upregulates p53 expression, bringing about apoptosis by directly binding to TP53 gene promoter, but the transcription factor remains unknown. p53 can bind to the YAP promoter and upregulate YAP expression as well.
Cell proliferation

Uncontrolled cell proliferation is often the first step in the development of cancer. The inhibition of cell proliferation by activation of the Hippo pathway was established as early as it was discovered. Under physiological conditions, the Hippo pathway is well established for size control of organs (3). This trait was initially applied in regenerative medicine to promote regeneration of damaged tissues and proliferation of stem cells by activating YAP. Specific mechanisms include inhibition of differentiation, expansion of the stem cell pool, as well as reprogramming differentiated cells into a more primitive and stem cell-like progenitor cell state (86). It has been confirmed that in developing skin, ectopic YAP activation causes decreased expression of differentiation markers (Krt1, Ivl and Lor) and increased expression of progenitor cell markers (87). Another important effect is its involvement in facilitating the entry of non-dividing cells or quiescent cells into the cell cycle. Activation of YAP/TAZ has been applied to stem cell expansion in injured intestine, oval cell expansion, hepatocyte injury, and even regeneration of the cardiomyocyte after myocardial infarction (88,89), which is one of the typical quiescent cells.

It was subsequently found that this function and cancer development are also closely related. When the Hippo pathway kinase is mutated and loses its inhibitory effect on YAP/TAZ, YAP/TAZ promote the growth of cells and the tumorigenic potential by binding to TEADs and mediating the downstream target genes, including growth promoter such as ANKRDI (90), Fos (91), cell cycle regulators such as FoxM1 (92), p27 (93), and apoptosis regulator such as Diapl (94), NR4A1 (95). Accordingly, YAP is frequently amplified or overactivated in some human solid tumors. The truth is the stem cell properties, or ‘stemness’, conferred by YAP, finally leads to tumorigenesis plus other pro-tumorigenic events (88).

The process of YAP activation leading to tissue overgrowth and tumor formation is reversible after cessation of YAP activation (9). Therefore, this finding provides a solution to balance the treatment of damaged tissues with the prevention of tumorigenesis. As noted by Moya et al. (88), there existed a therapeutic window of YAP/TAZ activation that could be used to induce regeneration while avoiding organ overgrowth.

Hippo-YAP-regulated tumor immunity

The Hippo-YAP pathway is not only associated with cell proliferation, but also implicated in the suppression of host antitumor immune response, including both innate immunity and adaptive immunity. Rather through the canonical path, many molecules in the Hippo-YAP pathway regulate immune cell activity and function independently. First, in terms of innate immunity, the Hippo-YAP pathway plays an important role in anti-tumor response through detecting tumor DNA, inducing IFN-1, pro-inflammatory cytokines and chemokines, recruiting inflammatory cells, and subsequently stimulating adaptive immune responses (96,97). Genes related to the Hippo-YAP pathway include S1PR1, PDGFB, and NLRP3 (98); pro-inflammatory cytokines and their receptors include IL1α/β, IL8, CXCR4, CXCL1/2/3/5, CCL2, and CSF1 (98-100); complement factors include CFI, C3 (98), and cells include myeloid-derived suppressor cells (MDSCs) (101), tumor-associated macrophages (TAMs) and M2 macrophages (102).

The Hippo pathway functions in tumorigenesis through regulating the tumor immune microenvironment rather than intra-tumor cell signaling. On the one hand, the Hippo-YAP pathway can be activated by innate immune receptors. Some innate immune receptor ligands, such as pol (I:C), LPS and CpG, are efficient anti-tumor agents, which can induce strong activation of IFN signaling and activation of the Hippo-YAP pathway (103). On the other hand, Hippo-YAP pathway dysregulation can in turn lead to cancer development through YAP accumulation and inhibition of anti-tumor response. Wang et al. (101) found that in a murine prostate adenocarcinoma model, YAP directed MDSCs to tumor sites via the CXCL5-CXCR2 axis to help establish the TME. In a murine liver tumor model, Hagenbeek et al. (104) also identified that TAZ induced myeloid cell infiltration and pro-inflammatory cytokine secretion. Apart from that, YAP can either direct TAMs differentiation to an immunosuppressive/“pro-tumor” M2 phenotype or directly recruit M2 macrophages to suppress immune clearance (105). In most cases, the Hippo signaling is a positive factor in the innate immune response, but with the establishment of the TME, YAP/TAZ dismisses the role of the Hippo signaling in anti-tumor immune responses.

Second, in adaptive immunity, many clinical successes have dictated that anti-tumor immunity is T-cell centered (96). Rather than function in the TME, YAP/TAZ directly regulate immune cells, of which the T cell is the main victim. Disruption of MST1/2 significantly reduces the level of peripheral T cells and impairs the function of T cells (97,106). Overexpression of YAP induces...
differentiation of CD4+ T lymphocytes to Regulatory T cells (Treg) (107) and also negatively regulates the proliferation of CD4+ T lymphocytes (108). Same with the Hippo-YAP pathway, Tregs are also characterized by the Yin-Yang dynamics in cancer, as they suppress inflammation-driven tumorigenesis by restraining inflammation, whereas their ability to curb inflammatory cells encourages non-inflammatory tumorigenesis. The “unproductive” immunosuppression even leads to cancer progression (109). Ni et al. (110) reported that YAP was highly expressed in Tregs and enhanced Treg production through the activin-activin receptor signaling axis, causing it to enrich in the tumor. Transcriptional regulation of the star molecule programmed death ligand-1 (PD-L1) gene is another important mechanism for YAP/TAZ to regulate T cells. PD-L1 is constitutively expressed on the surface of cancer cells, while the receptor of PD-L1, programmed death protein-1 (PD-1), is mostly expressed on the surface of T cells. Therefore, the interaction between them prevents cancers cells from immune surveillance of T cells (111). YAP/TAZ and PD-L1 have a bidirectional interaction in suppressing anti-tumor T cell responses. Not only does YAP/TAZ directly upregulate the expression of PD-L1 (97,112), but the overexpression of PD-L1 also effectively increases the level and transcriptional activity of YAP (113).

The first paradox is the relationship between MST1 and Tregs. As an upstream inhibitory molecule of YAP/TAZ, MST1 is supposed to perform the opposite function to YAP; but it turns out that MST1 can yet enhance Treg function (114) and its deficiency results in autoimmune diseases due to impaired Tregs (115).

The second paradox, also the most concerned, is the finding in an article (116) published in Cell. The authors first observed that the loss of LATS1/2 significantly inhibited tumor growth in a variety of cancer types in mice, e.g., melanoma, breast cancer, squamous cell carcinoma. LATS1/2 are a pivotal factor with growth inhibitory/tumor-suppressive functions in the Hippo signaling, but without LATS1/2, tumor cells secret nucleic acid-rich EVs to promote TLRs-Myd88/TRIF signaling and type I IFN production, thereby accelerating DC maturation, CD8+ T lymphocyte expansion, and tumor growth arrest (116). Thus, LATS1/2 depletion stimulates the activity of innate and adaptive immunity to completely destroy the TME, resulting in strong anti-tumor immunity. Besides, the researchers added that under physiological conditions, the inhibition of LATS and activation of YAP during wound healing and tissue regeneration both promoted cell proliferation and prevented overgrowth and metastasis from an immunosurveillance perspective. This view complements the above account of the relationship between the Hippo pathway and cell proliferation. Nevertheless, there are limitations to the article. The first is that it acknowledged that the relationship between the Hippo pathway and immune cells in mouse models could not be reproduced in human cancer for the time being (116). Similarly, regarding the relationship between YAP/TAZ and PD-L1 in human cancers, Janse van Rensburg et al. (117) also found that the phenomenon could not be identified in mouse cell lines. Taha et al. (97) made a conjecture that there were species-specific differences in the transcriptional targets of the above molecules. Comparing the Hippo-YAP pathway across species might be a good direction to solve the problem. The second is, other articles (105,118) hold converse standpoints: knockout of LATS1/2 recruited type II macrophages and established an immunosuppressive microenvironment. The difference lies in the properties of the animal model of different cancers. In addition to species specificity, there is also tumor specificity in the Hippo-YAP pathway, which has been mentioned in some of the contradictory points above.

Conclusions and future prospect

In this investigation, the aim was to assess recent advance of the Hippo-YAP pathway in oncology and analyze the contradictions that have emerged over the years in a wide range of literature. Considering that all these contradictions have a solid experimental basis, the Hippo pathway should not be simply categorized as a tumor suppressive pathway (Yin) or a tumor promoting pathway (Yang), but should be fully investigated from the view of the Yin-Yang dynamics. More recently, a series of controversial studies (119,120) on breast cancer and the Hippo pathway have been published in Nature. Ma et al. (119) found that LATS1/2 promoted the growth of ERα+ breast cancer cells by maintaining ERα expression, while over-activation of YAP/YAZ was sufficient to inhibit ERα expression, challenging the findings of Britschgi et al. (121) in 2017. Britschgi et al. replied to their query, suggesting that the differences could stem from different subclones, experimental methods, culture conditions, etc. They also acknowledged that LATS1/2 should not be recognized simply as a tumor suppressor. Although the pathogenesis of breast cancer was well established and the literature was published in topical journals, four years later the researchers (119) still
found a surprising and paradoxical role in breast cancer for one of the Hippo pathway molecules. Thus, we can infer that with many new theories about cancer being proposed, more mechanisms and contradictions of Hippo pathway regulation of cancer will keep coming out in the future. This brings us opportunities for curing cancer and challenges in practical applications at the same time. Many reviews have mentioned that it is yet unknown how to curb YAP/TAZ activation safely and effectively in human patients, and that YAP/TAZ inhibition may have unintended consequences (89,122). However, there is a silver lining: if a therapeutic window for YAP/TAZ activators can be explored in the future, and if YAP/TAZ activators are moderately applied, it is very likely that both the oncogenic potential of YAP/TAZ will be eliminated and the potential of organ regeneration will be fulfilled.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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