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Review

Research progress of the Hippo signaling pathway in renal cell carcinoma

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Abstract *Objective:* This review aimed to summarize the role of the Hippo signaling pathway in renal cell carcinoma (RCC), a urologic malignancy with subtle initial symptoms and high mortality rates due to metastatic RCC. The Hippo signaling pathway, which regulates tissue and organ sizes, plays a crucial role in RCC progression and metastasis. Understanding the involvement of the Hippo signaling pathway in RCC provides valuable insights for the development of targeted therapies and improved patient outcomes.
Methods: In this review, we explored the impact of the Hippo signaling pathway on RCC. Through an analysis of existing literature, we examined its role in RCC progression and metastasis. Additionally, we discussed potential therapeutic strategies targeting the Hippo pathway for inhibiting RCC cell growth and invasion. We also highlighted the importance of investigating interactions between the Hippo pathway and other signaling pathways such as Wnt, transforming growth factor-beta, and PI3K/AKT, which may uncover additional therapeutic targets.
Results: The Hippo signaling pathway has shown promise as a target for inhibiting RCC cell growth and invasion. Studies have demonstrated its dysregulation in RCC, with altered expression of key components such as yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ). Targeting the Hippo pathway has been associated with suppressed tumor growth and metastasis in preclinical models of RCC. Furthermore, investigating crosstalk between the Hippo pathway and other signaling pathways has revealed potential synergistic effects that could be exploited for therapeutic interventions.
Conclusion: Understanding the role of the Hippo signaling pathway in RCC is of paramount importance. Elucidating its functions and molecular interactions contributes to RCC diagnosis, treatment, and the discovery of novel mechanisms. This knowledge informs the development of innovative therapeutic strategies and opens new avenues for research in RCC. Further

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investigations are warranted to fully comprehend the complex interplay between the Hippo pathway and other signaling pathways, ultimately leading to improved outcomes for RCC patients.

1. Introduction

Kidney cancer is a prevalent malignancy within the urologic system. In terms of worldwide cancer statistics, kidney cancer ranks the 14th overall (the 9th position among males and the 14th position among females), with renal cell carcinoma (RCC) comprising approximately 90% of cases, underscoring the significance of studying RCC as a major health concern [1]. Despite the stable mortality rate, a substantial number of individuals succumbed to RCC globally in 2020. It is estimated that approximately 179 368 patients (115 600 males and 63 768 females) lost their lives due to this disease [2]. These statistics highlight the continued impact of RCC as a significant cause of mortality. Metastatic RCC (mRCC) continues to be the leading cause of mortality, despite significant advancements in immune checkpoint inhibitors and targeted therapies which have made notable contributions to improving disease-free survival among mRCC patients [3—5]. Nonetheless, the effective management of metastatic disease remains a prominent concern in clinical practice [6,7]. Although the mortality rate for RCC is gradually decreasing, the incidence of RCC is rising in developed countries. Moreover, this malignancy continues to pose a significant threat to individuals residing in undeveloped and developing nations and the escalating morbidity rates highlight the ongoing burden posed by RCC on a global scale [2].

The Hippo signaling pathway represents an evolutionarily conserved adaptive signaling mechanism that maintains the size of tissue and organs. It achieves this by regulating essential cellular processes such as cell proliferation, apoptosis, and the self-renewal or differentiation of stem cells [8]. The initial discovery that mutations in the Hippo signaling pathway caused tissue overgrowth in *Drosophila melanogaster* generated significant interest among researchers regarding its potential implications in tumorigenesis [9,10]. This finding sparked a strong curiosity about the influence of the Hippo signaling pathway on tumor development. The Hippo signaling pathway comprises a complex protein network in which enzymes and functional proteins play crucial roles in various tissue. This intricate network controls the growth and regeneration of diverse organs and significantly impacts the prognosis of diseases, including cancers. Mutations in the Hippo signaling pathway are frequently observed in various human tumors [9]. However, these mutations do not solely occur in genes. Additionally, there is significant crosstalk between the Hippo signaling pathway and other signaling pathways or tumor mechanical characteristics, which can influence its function [10,11,12].

Currently, it is widely recognized that dysregulation of the Hippo signaling pathway plays a significant role in tumor progression. The malfunction of this pathway has been implicated in various aspects of tumorigenesis [13,14]. A considerable number of studies have been published on the Hippo signaling pathway, uncovering new molecules that play significant roles in this pathway. However, there is currently a lack of comprehensive reviews focusing specifically on the relationship between RCC and the Hippo signaling pathway. To address this gap, the present study aimed to collect and review the research conducted in recent years exploring the connection between RCC and the Hippo signaling pathway. This study aimed to provide researchers in the fields of RCC and the Hippo signaling pathway with a solid foundation and valuable insights for future investigations.

2. The Hippo signaling pathway

2.1. Molecular components of the Hippo signaling pathway

The Hippo signaling pathway primarily plays its role through a kinase cascade reaction involving a core cassette [15]. This cassette comprises several key components, including mammalian sterile-20-like kinase 1, mammalian sterile-20-like kinase 2, Salvador 1 (SAV1), large tumor suppressor kinase 1/2 (LATS1/2), MOB kinase activator 1, yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ), and the TEAD/TEF family [16]. In the cell nucleus, these molecules interact to regulate various cellular processes [17]. A comprehensive classification of genes related to the Hippo signaling pathway can be found in Table 1.

2.2. Mechanisms of the Hippo signaling pathway regulation of cell proliferation

At low cell density, the Hippo signaling pathway remains inactive, and there is no contact inhibition between cells. However, when growth factors, such as endothelial growth factors, insulin-like growth factors, and vascular endothelial growth factors, are present, they activate the growth factor signaling pathway by interacting with receptor tyrosine kinases. This activation leads to sequential phosphorylation of the downstream Ras—RAF—MEK—ERK cascade reaction. Consequently, the activity of the Hippo core cassette is inhibited [18]. Simultaneously, the activation of receptor tyrosine kinases also stimulates the PI3K—AKT pathway. The downstream effector of this pathway, 3-phosphoinositide dependent protein kinase 1, further inhibits the Hippo core cassette [19]. Furthermore, G-protein coupled receptor signaling pathways have the ability to regulate cellular cytoskeleton function. This regulation leads to the inhibition of YAP/TAZ

Table 1 The genetic components of the Hippo signaling pathway.

Category	Gene
Major functional gene	*MST1/2*, *SAV1*, *LATS1/2*, *YAP1*, *WWTR1*, *AMOT*, and *FRMD6*
Nuclear signaling molecule	*YAP1*, *WWTR1*, *SMAD2–4*, *TCF7*, *TCF7L 1/2*, *LEF1*, *SOX2*, *MYC*, and *CCND 1–3*
Adenylate cyclase	*PPP2CA*, *PPP2R1A*, and *PPP2R2B*
Protein kinase	*PRKCZ*, *PRKCI*, *LATS1/2*, *STK3*, *CSNK1D*, *CSNK1E*, *BMPR1A*, *BMPR1B*, *BMPR2*, and *GSK3B*
Adenylate cyclase inhibitor	*SMAD7*
Cell adhesion molecule	*CDH1*, *FZD1-10*, *CTNNA1*, and *ITGB2*
Cell polarity protein	*PARD3*, *PARD6*, *INADL*, *MPP5*, *LGL*, *SCRIB*, and *DLG1–5*
Signal transduction regulator	*CRB1*, *AMOT*, *FRMD1*, *FRMD6*, *SAV1*, *RASSF6*, *RASSF1*, *CTGF*, *GLi2*, *AREG*, *BIRC5*, *AFP*, *TGFB1–3*, *BMP2*, *BMP4–8*, *GDF5–7*, and *AMH*

MST1/2, mammalian sterile 20-like kinase 1/2; *SAV1*, Salvador 1; *LATS1/2*, large tumor suppressor kinase 1/2; *YAP1*, yes-associated protein 1; *WWTR1*, WW omain-containing transcription regulator 1; *AMOT*, angiomotin; *FRMD*, FERM domain-containing protein; *SMAD*, mothers against decapentaplegic homolog; *TCF7*, transcription factor 7; *TCF7L 1/2*, *TCF7*-like 1/2; *LEF1*, lymphoid enhancer-binding factor 1; *SOX2*, SRY-box transcription factor 2; *MYC*, Myc proto-oncogene protein; *CCND1–3*, G1/S-specific cyclin-D 1–3; *PPP2CA*, protein phosphatase 2 catalytic subunit A alpha; *PPP2R1A*, protein phosphatase 2 scaffold subunit alpha; *PPP2R2B*, protein phosphatase 2 regulatory subunit B beta; *PRKCZ*, protein kinase C zeta type; *PRKCI*, protein kinase C iota type; *STK3*, serine/threonine-protein kinase 3; *CSNK1D*, casein kinase 1 isoform delta; *CSNK1E*, casein kinase 1 isoform epsilon; BMP, bone morphogenetic protein; *BMPR1A*, BMP receptor type-1A; *BMPR1B*, BMP receptor type-1B; *BMPR2*, BMP receptor type-2; *GSK3B*, glycogen synthase kinase-3 beta; *CDH1*, cadherin 1; *FZD1–10*, Frizzled class receptor 1–10; *CTNNA1*, catenin alpha 1; *ITGB2*, integrin beta-2; *PARD3*, partitioning defective 3 homolog; *PARD6*, partitioning defective 6 homolog; *INADL*, InaD-like protein; *MPP5*, membrane palmitoylated protein 5; *LGL*, lethal giant larvae 1; *SCRIB*, scribble planar cell polarity protein; *DLG1–5*, disks large homolog 1–5; *CRB1*, crumbs cell polarity complex component 1; *RASSF*, Ras association domain-containing protein; *CTGF*, connective tissue growth factor; *GLi2*, GLI family zinc finger 2; *AREG*, amphiregulin; *BIRC5*, baculoviral IAP repeat-containing protein 5; *AFP*, alpha-fetoprotein; *TGFB1–3*, transforming growth factor beta 1–3; *GDF5–7*, growth/differentiation factor 5–7; *AMH*, anti-Mullerian hormone.

phosphorylation by LATS1/2 [20]. In this scenario, when YAP/TAZ is not phosphorylated by the Hippo core cassette or other molecules, it can directly translocate into the cell nucleus. Within the nucleus, YAP/TAZ interacts with downstream transcription factors, such as TEADs. This interaction leads to the activation of target gene transcription, thereby promoting cell growth and proliferation [21,22].

In contrast, when cells reach a high density, the signaling dynamics change significantly. While the receptor tyrosine kinase pathway remains inactive, adenosine monophosphate-activated protein kinase in the cytoplasm can directly phosphorylate YAP/TAZ. This phosphorylation event leads to the activation of the Hippo kinase core. In the context of contact inhibition, when the G-protein coupled receptor pathway is activated, it inhibits Rho GTPases solely through $G\alpha_s$. This action leads to the reversal of cytoskeleton regulation and subsequently relieves the inhibition on LATS1/2. As a consequence of the activated kinase core, LATS1/2 phosphorylates YAP/TAZ, making it challenging for it to translocate into the cell nucleus and exert further effects. Consequently, cell growth and proliferation are inhibited.

Furthermore, numerous factors and proteins exert complex multidimensional effects on YAP/TAZ. For instance, proteins involved in cell polarity, such as zona occludens proteins and α-catenin, can suppress YAP/TAZ expression or activity [23,24]. Conversely, angiomotin can activate it [25]. In the realm of cell density, annexin A2, E-cadherin, and Kin of IRRE-like protein 1 (KIRREL1) function as inhibitors, whereas partition defective protein 1b (PAR1b) promotes YAP/TAZ expression [26–29]. These intricate interactions underscore the importance of comprehensively understanding the myriad regulatory mechanisms of YAP/TAZ in various physiological and pathological contexts.

When it comes to stress signals, the underlying mechanisms can be quite intricate. For instance, hypoxia triggers the activation of zyxin, seven in absentia homolog 2 (SIAH2), and hypoxia-inducible factor-alpha (HIF-α), which have the potential to activate YAP/TAZ in various ways [30]. Similarly, energy stress prompts the activation of the adenosine monophosphate-activated protein kinase signaling pathway, leading to a downregulation of YAP/TAZ [31]. Heat stress, on the other hand, stimulates heat-shock protein 90, ultimately activating YAP/TAZ [32]. Lastly, endoplasmic reticulum stress activates growth arrest and DNA damage-inducible 34/protein phosphatase 1 (GADD34/PP1), which results in a down-expression of YAP/TAZ [33]. These diverse stress-induced regulatory mechanisms underscore the dynamic and complex nature of YAP/TAZ regulation in response to various environmental insults.

Moreover, mechanical cues play a pivotal role in the regulation of YAP/TAZ expression. Tension, cell adhesion, fluid flow, the stiffness of the extracellular matrix, and even changes in geometry all contribute significantly to the modulation of YAP/TAZ expression [34–38]. These mechanical inputs serve to integrate the biophysical environment with the intracellular signaling networks, thereby fine-tuning the activity of YAP/TAZ and ultimately influencing cellular responses and fate decisions.

From the mechanism of the Hippo signaling pathway, it becomes evident that YAP/TAZ plays a central role in the

entire pathway. Therefore, this study categorizes the mechanisms of the Hippo signaling pathway regulation in RCC into two categories: YAP/TAZ-mediated and non-YAP/TAZ mediated regulatory mechanisms.

3. YAP/TAZ-mediated RCC regulation process

3.1. YAP/TAZ-mediated RCC growth and proliferation

Indeed, extensive research has been conducted on YAP/TAZ in the context of RCC. Overexpression of *YAP* gene has been observed in clear cell RCC (ccRCC) tissue. Furthermore, experimental studies involving the knockdown of *YAP* have demonstrated its role in inhibiting cell proliferation, inducing cell cycle arrest, and promoting apoptosis [39,40]. Xu et al. [41] reported that the knockdown of *YAP* in RCC cells inhibits their angiogenic capacity. Additionally, YAP has been shown to stimulate the expression of vascular endothelial growth factor A, with GLI family zinc finger 2 being involved in this process. Yang et al. [42] conducted a study demonstrating that cell density, which is closely linked to the Hippo signaling pathway, influences the occurrence of ferroptosis in RCC. They observed that TAZ activation occurs in early passage RCC cell lines and regulates the sensitivity of ferroptosis through the TAZ-EMP1-NOX4 pathway. In a study by Xu et al. [43], it was reported that the overexpression of apolipoprotein M inhibits the growth and proliferation of ccRCC. This regulation occurs through apolipoprotein M's influence on the stability of YAP and subsequent modulation of YAP expression in ccRCC.

3.2. YAP/TAZ-mediated RCC invasion and metastasis

The invasion and metastasis of RCC are crucial factors that greatly impact patient prognosis. Therefore, understanding the influence of the Hippo signaling pathway on the invasion and metastasis of RCC holds significant importance. Chen et al. [44] conducted a study revealing that shear stress plays a role in regulating RCC extravasation and metastasis. Notably, they found that YAP1 functions as a mechanosensor, converting mechanical stimuli into cellular signals in conditions of low shear stress. This mechanotransduction process ultimately promotes RCC metastasis. Meng et al. [45] conducted an analysis using The Cancer Genome Atlas (TCGA) and Clinical Proteomic Tumor Analysis Consortium (CPTAC) databases, revealing that EF-hand domain family member D1 (*EFHD1*) is down-regulated in RCC. However, patients with higher levels of *EFHD1* exhibit improved overall survival in ccRCC. Overexpression of *EFHD1* leads to a significant reduction in intracellular mitochondrial Ca^{2+}, binding to the mitochondrial calcium uniporter and deactivating the Hippo/YAP signaling pathway, which in turn diminishes the migration, invasion, and metastasis capabilities of RCC. These findings have significant implications for tumor invasiveness and metastasis.

3.3. YAP/TAZ-mediated upstream and downstream mechanisms in RCC

In addition to the direct investigation of YAP/TAZ in RCC, numerous studies have explored the upstream and downstream mechanisms associated with YAP/TAZ. These investigations aimed to unravel the intricate network of molecular pathways that regulate the activity of YAP/TAZ in RCC. Xiao et al. [46] employed mass spectrometry to identify arrestin domain containing (ARRDC) 3 and ARRDC1 as interacting partners of YAP1 in RCC. They demonstrated that ARRDC1 and ARRDC3 play a crucial role in regulating YAP1 by promoting its degradation. This regulation occurs through the itchy E3 ubiquitin protein ligase (Itch)-mediated ubiquitination process. The findings establish ARRDC1 and ARRDC3 as essential regulators of YAP1 in RCC. Kumar et al. [47] undertook a comprehensive series of studies focusing on claudin-2, a protein highly expressed in the proximal tubular epithelium of the kidney (the origin of ccRCC). Their findings revealed that claudin-2 can interact with YAP, influencing the phosphorylation and nuclear translocation of YAP. This research demonstrates the synergistic relationship between claudin-2 and the Hippo signaling pathway in counteracting RCC. Liu et al. [48] confirmed a positive correlation between long non-coding RNA (lncRNA) *TUG1* and YAP in RCC. Their study revealed that over-expressing lncRNA *TUG1* increased YAP levels, without affecting the activity of the Hippo signaling pathway or the cellular localization of YAP in RCC. By investigating the competing endogenous RNA mechanism, they uncovered that microRNA (miRNA)-9 can bind to lncRNA *TUG1*, resulting in the down-regulation of lncRNA *TUG1* expression. This down-regulation, in turn, positively regulated YAP. Zhang et al. [49] discovered that miRNA-335, an anti-tumor RNA, is down-regulated in RCC. Through their investigation, they confirmed lysine demethylase 3A (KDM3A) as a downstream signaling molecule of miRNA-335. Their findings revealed that the expression of YAP increases with the up-regulation of KDM3A, thus establishing a regulatory axis involving miRNA-335/KDM3A/YAP. Wu et al. [50] made a bioinformatic analysis and identified fragile X mental retardation 1 (*FMR1*) as a gene that exhibited a close connection with YAP/TAZ and displayed a positive correlation with immune cell infiltration. They and Yuan and Li [51] performed an immunohistochemistry to verify that *FMR1* is indeed highly expressed in the ccRCC tissue, suggesting that *FMR1* could serve as a potential novel biomarker in ccRCC.

3.4. YAP/TAZ as a signaling hub for multiple pathways

The signaling pathways involved in RCC are intricate and interconnected, indicating the presence of complex

relationships between the Hippo signaling pathway and other pathways. Understanding these intricate interactions is crucial for unraveling the comprehensive molecular landscape of RCC. White et al. [52] conducted a comprehensive study examining the role of YAP/TAZ in neurofibromatosis type 2 (*NF2*)-deficient RCC. Their research unveiled that YAP/TAZ plays a crucial role in the PI3K—AKT signaling pathway, promoting glycolysis in *NF2*-deficient RCC. Furthermore, they discovered that YAP/TAZ inhibits mitochondrial respiration, leading to the production of reactive oxygen species and subsequent cell death under nutrient stress conditions. Interestingly, when YAP/TAZ is inactivated, it triggers compensatory activation of the lysosomal-mediated mitogen-activated protein kinases (MAPKs) signaling pathway, enabling RCC cells to continue proliferating and surviving. Therefore, a combined inhibition strategy targeting both the YAP/TAZ and TEAD1—Twist1 MAPK pathway may effectively impede the growth of *NF2*-deficient RCC. Zhu et al. [53] reported on the regulatory role of the RNA binding protein Quaking (QKI) in YAP, influencing cellular contact inhibition in RCC. Notably, QKI was found to inhibit the proliferation and aggressiveness of RCC through modulation of the Wnt pathway and G-protein coupled receptor pathway.

4. Non-YAP/TAZ-mediated RCC regulation process

4.1. The role of other important molecules in the regulation of RCC within the Hippo signaling pathway

Indeed, besides YAP/TAZ, the Hippo signaling pathway encompasses several other crucial molecules, including SAV1 and NF2. These molecules play significant roles in mediating the activity and regulation of the Hippo signaling pathway. A significant down-regulation of SAV1 in high-grade ccRCC at an early stage has been reported [54,55]. Their findings revealed that the activation of YAP1 in renal proximal tubular epithelial cells facilitated cell growth and proliferation, ultimately contributing to the development of ccRCC. Guan et al. [56] made a notable discovery that the knockdown of miRNA-572 targeted the NF2/Hippo signaling pathway, resulting in the suppression of RCC proliferation and promoting RCC apoptosis. Kidney and brain expressed protein (KIBRA) has been identified as a regulatory component upstream of the Hippo signaling pathway [57]. Schelleckes et al. [58] proposed that the down-regulation of KIBRA in ccRCC is attributed to promote DNA methylation. They suggested that the process of promote methylation alters the balance of *KIBRA*/specificity protein 1 binding, potentially contributing to the development and progression of ccRCC.

4.2. Exploring the potential role of molecules within the Hippo signaling pathway

Furthermore, several studies have confirmed or revealed novel molecules or mechanisms that expand our understanding of the Hippo signaling pathway. Miao et al. [59] reported that dihydrolipoamide branched chain transacylase E2, a tumor suppressor, exhibits low expression in ccRCC due to methyltransferase-like protein 3 (METTL3)-mediated N6-methyladenosine (m^6A) modification. Their study elucidated that dihydrolipoamide branched chain transacylase E2 activates the Hippo signaling pathway and corrects lipid metabolism disorder, thereby exerting inhibitory effects on cancer progression. Yin et al. [60] identified a novel molecule called SH3 domain binding glutamate-rich protein like 2 (SH3BGRL2) that has the ability to activate the Hippo/TEAD1—Twist1 signaling pathway, resulting in the suppression of ccRCC growth. Yu et al. [61] demonstrated that the knockout of pleckstrin homology domain containing O1 (*PLEKHO1*) can effectively inhibit ccRCC cell viability, induce cell apoptosis, and prevent ccRCC formation *in vivo*. These effects were mediated through the Hippo signaling pathway or MAPK/JNK (c-Jun N-terminal kinase) pathway.

4.3. Mechanisms of Hippo signaling pathway regulation in RCC drug resistance

The advent of targeted drugs has significantly extended the overall survival of patients with mRCC. However, drug resistance poses a significant challenge to the long-term survival of patients undergoing targeted therapy. In order to address this issue, researchers have dedicated considerable efforts to study the Hippo signaling pathway as a potential avenue for overcoming drug resistance in mRCC. Peng et al. [62] conducted a study on Frizzled-1 (FZD1), a receptor of the Wnt signaling pathway, in the context of RCC. Their findings revealed that FZD1 exhibited high expression levels in RCC, RCC cell lines, and sunitinib-resistant cell lines. Importantly, the expression of FZD1 was found to be predictive of the recurrence, metastasis, pathological stage, and prognosis in patients with RCC. Furthermore, through Kyoto Encyclopedia of Genes and Genomes enrichment analysis, it was speculated that FZD1 might have a significant correlation with the Hippo signaling pathway. Jiang et al. [63] discovered that SAV1 has the ability to bind with AKT, thereby inhibiting its activity. However, in RCC, mutations in SAV1 prevent its interaction with AKT, resulting in the excessive activation of AKT. This aberrant activation is facilitated by the involvement of Mer tyrosine kinase (MerTK). Consequently, RCC exhibits increased aggressiveness and develops resistance to therapeutic drugs.

5. The value of the Hippo signaling pathway in the classification and prognosis of RCC

Through our comprehensive literature review, it has become evident that the Hippo signaling pathway exhibits a significant correlation with renal mucinous tubular and spindle cell carcinoma (MTSCC), a distinct subtype of RCC. MTSCC is characterized by the presence of elongated tubules lined with cords of cuboidal and spindle cells, accompanied by an abundant mucus stroma [64]. MTSCC displays a remarkable degree of consistency concerning its immunophenotypic and cytogenetic abnormalities [65].

5.1. The Hippo signaling pathway guides the classification of MTSCC

Mehra et al. [66] conducted a comprehensive analysis of renal MTSCC by performing complete exome and transcriptome sequencing on a cohort of 22 patients. Their study revealed that a significant proportion (85%) of the MTSCC samples exhibited alterations in genes related to the Hippo signaling pathway. Furthermore, they observed overexpression of the YAP1 nuclear protein, a key component associated with the Hippo signaling pathway, in the majority of cases (90%). These findings strongly indicate that dysregulation of the Hippo signaling pathway plays a crucial role in the development of MTSCC. This knowledge underscores the importance of understanding the Hippo signaling pathway for accurate diagnosis and effective treatment strategies for this rare subtype of RCC. It also provides a solid foundation for further research and intervention approaches. It is worth noting that renal MTSCC shares histological and immunophenotypic features with type I papillary RCC. To further explore this similarity, Ren et al. [67] employed a high-resolution single nucleotide polymorphism array platform in their study. They conducted genome-wide copy number and allelic imbalance analyses on cases exhibiting comparable histological characteristics of MTSCC and papillary RCC. The research team uncovered a significant finding regarding the unusual regulation of the Hippo/YAP pathway, providing valuable insights into the molecular mechanisms underlying these two subtypes.

5.2. The Hippo signaling pathway guides the classification of rare subtypes of RCC

Unclassified RCC (uRCC) represents a significant proportion of invasive non-ccRCC cases [68,69]. However, a standardized treatment approach for this subtype has not yet been established [70,71]. In an effort to address this gap, Chen et al. [72] conducted gene sequencing, RNA sequencing, and single nucleotide polymorphism array analysis on a cohort of 62 high-grade primary uRCC cases. Through this comprehensive analysis, they discovered that 26% of the uRCC cases exhibited specific features including *NF2* deletion and dysregulation of the Hippo/YAP pathway. These findings not only led to the identification of a distinct uRCC subtype but also expanded the diagnostic and therapeutic strategies available for managing uRCC.

The Hippo signaling pathway holds significant importance in guiding the classification and prognosis of various histological types of RCC. Its relevance extends beyond specific

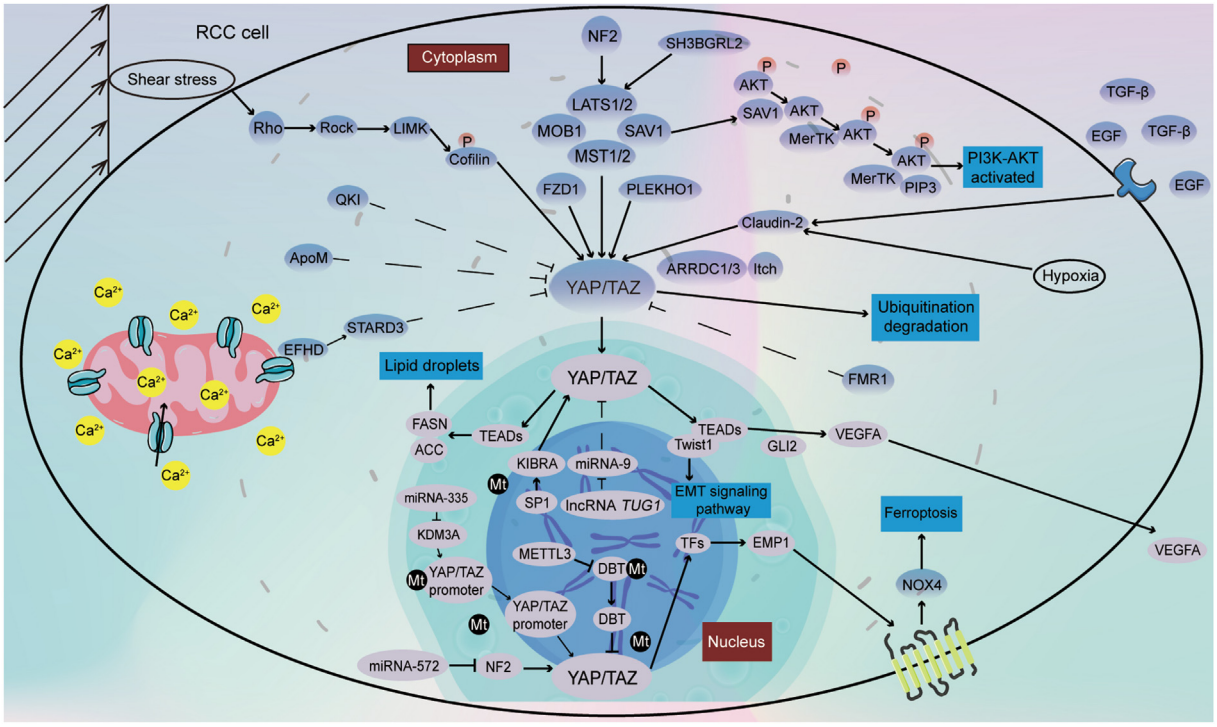

Figure 1 The mechanism of the Hippo signaling pathway in RCC. RCC, renal cell carcinoma; NF2, neurofibromatosis type 2; MST1/2, mammalian sterile-20-like kinase 1/2; SAV1, Salvador 1; LATS1/2, large tumor suppressor kinase 1/2; MOB1, MOB kinase activator 1; YAP, yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; FZD1, Frizzled-1; PLEKHO1, pleckstrin homology domain containing O1; ARRDC1/3, arrestin domain containing 1/3; Itch, itchy E3 ubiquitin protein ligase; MerTK, Mer tyrosine kinase; SH3BGRL2, SH3 domain binding glutamic acid-rich protein like 2; Rock, Rho-associated coiled-coil forming protein kinase; LIMK, LIM domain kinase; QKI, Quaking; ApoM, apolipoprotein M; EFHD, EF-hand domain family member D; STARD3, StAR-related lipid transfer domain containing 3; FMR1, fragile X mental retardation 1; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; KDM3A, lysine demethylase 3A; METTL3, methyltransferase-like protein 3; DBT, dihydrolipoamide branched chain transacylase E2; SP1, specificity protein 1; KIBRA, kidney and brain expressed protein; EMP1, epithelial membrane protein 1; NOX4, NADPH oxidase 4; GLi2, GLI family zinc finger 2; P, phosphorylation; M, methylation.

subtypes like MTSCC and uRCC, influencing the understanding and outcomes of other RCC histology as well. Malouf et al. [73] conducted a comprehensive study that elucidated the genomic landscape of sarcomatoid RCC (sRCC). Their research demonstrated that the Hippo signaling pathway is frequently altered in sRCC, indicating its crucial role in the pathogenesis of this aggressive subtype. Notably, they observed mutations within the Hippo signaling pathway that led to the nuclear accumulation of YAP/TAZ proteins. These findings suggest that targeting the Hippo signaling pathway could hold promise as a potential therapeutic strategy for the treatment of sRCC. In a study conducted by Duong et al. [74], an analysis of gene sets from ccRCC, papillary RCC, and chromophobe RCC was performed using data from TCGA. The researchers classified ccRCC into two groups based on the activity level of the Hippo signaling pathway: high-activity group and low-activity group. This investigation unveiled the prognostic significance of the Hippo signaling pathway in different histological subtypes of RCC. Specifically, patients with low Hippo signaling pathway activity exhibited a poorer prognosis. Zhang et al. [75] employed gene chips and bioinformatic analysis to investigate the presence of lncRNA and mRNA in the plasma of patients with ccRCC. Notably, their research identified the enrichment of non-regulatory mRNA within the Hippo signaling pathway. These findings shed light on the potential involvement of this pathway in ccRCC and its significance as a potential target for therapeutic interventions.

6. Conclusion and outlook

The mechanism of the Hippo signaling pathway in RCC can be more intuitively demonstrated in Figs. 1 and 2. Upon a comprehensive review of the literature, it is evident that the majority of studies have focused on understanding the mechanisms underlying the growth and proliferation of RCC, with relatively less emphasis on metastasis and drug resistance. The existing evidence strongly supports the involvement of the Hippo signaling pathway in tumor proliferation, indicating its significance in RCC. Therefore, there is a need to prioritize mechanistic studies exploring the regulation of the Hippo signaling pathway in RCC metastasis, as this may pave the way for future research in this area.

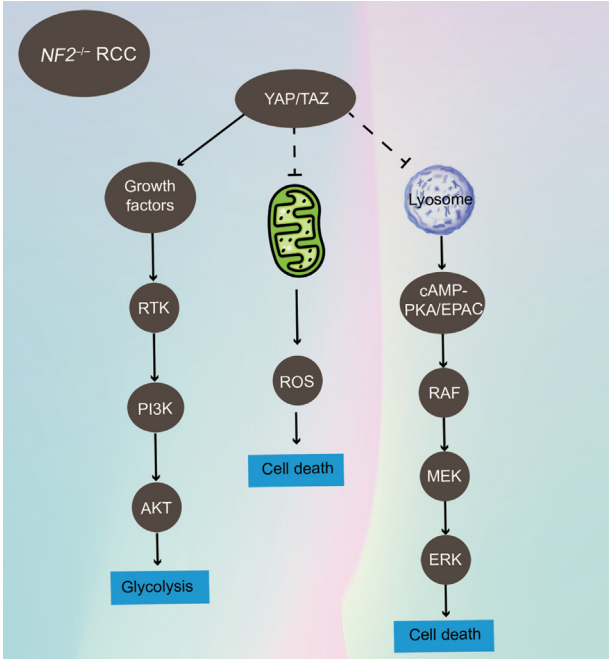

Figure 2 The mechanism of the Hippo signaling pathway in $NF^{-/-}$ RCC. *NF2*, neurofibromatosis type 2; RCC, renal cell carcinoma; RTK, receptor tyrosine kinase; ROS, reactive oxygen species; YAP/TAZ, yes-associated protein/transcriptional coactivator with PDZ-binding motif.

Furthermore, it is evident that the Hippo signaling pathway primarily acts as a tumor suppressor in RCC. However, it is important to acknowledge the limitations of targeting the Hippo signaling pathway therapeutically. Unlike many molecules targeted for treatment that are highly expressed in tumor cells, the Hippo signaling pathway tends to be under-expressed within these cells. Nevertheless, several clinical trials investigating therapeutic interventions targeting the Hippo signaling pathway have reported promising results. This suggests that utilizing inhibitors of the Hippo signaling pathway could hold potential in the treatment of cancer patients [76,77]. Moreover, verteporfin has demonstrated binding affinity for YAP, resulting in the disruption of its interaction with TEAD and consequently it has gained widespread utilization in the treatment of a diverse array of maladies, encompassing cancers, fibrotic disorders, and glaucoma [78]. It has demonstrated that first-in-class, first-in-human phase I clinical trial (NCT04665206) of VT3989, an inhibitor of YAP/TEAD, achieved a persistent anti-tumor response in patients with advanced malignant mesothelioma and other tumors with *NF2* mutations on the American Association for Cancer Research annual meeting website [79], which may present a promising probability of administering inhibitors of the Hippo signaling pathway in RCC patients. Besides, the antisense drug ION537 targeting YAP1 has entered phase I clinical trials (NCT04659096) and the oral inhibitor IK-930 (NCT05228015) targeting TEAD has also entered clinical trials.

Hence, additional investigations are necessary to explore effective methods targeting the Hippo signaling pathway specifically in tumor cells. Remarkably, significant mutations or dysregulations of the Hippo signaling pathway have been identified in several rare subtypes of RCC, such as MTSCC and sRCC, as mentioned in this study. This presents an intriguing area for further research.

In conclusion, further studies are warranted to unravel the regulatory mechanisms of the Hippo signaling pathway in the growth, proliferation, and drug resistance of RCC. Additionally, increased investment is needed to develop efficacious therapeutic agents targeting the Hippo signaling pathway in RCC.

Author contributions

Study concept and design: Yiren Yang, Linhui Wang.
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Data analysis: Yiren Yang, Wei Zhang.
Drafting of manuscript: Yiren Yang, Xinxin Gan, Wei Zhang.
Critical revision of the manuscript: Linhui Wang, Xinxin Gan, Wei Zhang, Xiaolei Shi.

Conflicts of interest

The authors declare no conflict of interest.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2021;71:209—49.

[2] Bukavina L, Bensalah K, Bray F, Carlo M, Challacombe B, Karam JA, et al. Epidemiology of renal cell carcinoma: 2022 update. Eur Urol 2022;82:529—42.

[3] Barata PC, Rini BI. Treatment of renal cell carcinoma: current status and future directions. CA Cancer J Clin 2017;67:507—24.

[4] Bakouny Z, El Zarif T, Dudani S, Connor Wells J, Gan CL, Donskov F, et al. Upfront cytoreductive nephrectomy for metastatic renal cell carcinoma treated with immune checkpoint inhibitors or targeted therapy: an observational study from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur Urol 2023;83:145—51.

[5] Bedke J, Albiges L, Capitanio U, Giles RH, Hora M, Lam TB, et al. The 2021 updated European Association of Urology guidelines on renal cell carcinoma: immune checkpoint inhibitor-based combination therapies for treatment-naive metastatic clear-cell renal cell carcinoma are standard of care. Eur Urol 2021;80:393—7.

[6] Sung WW, Ko PY, Chen WJ, Wang SC, Chen SL. Trends in the kidney cancer mortality-to-incidence ratios according to health care expenditures of 56 countries. Sci Rep 2021;11:1479. https://doi.org/10.1038/s41598-020-79367-y.

[7] Rathmell WK, Rumble RB, Van Veldhuizen PJ, Al-Ahmadie H, Emamekhoo H, Hauke RJ, et al. Management of metastatic clear cell renal cell carcinoma: ASCO guideline. J Clin Oncol 2022;40:2957—95.

[8] Wu Z, Guan K. Hippo signaling in embryogenesis and development. Trends Biochem Sci 2021;46:51—63.

[9] Cunningham R, Hansen CG. The Hippo pathway in cancer: YAP/TAZ and TEAD as therapeutic targets in cancer. Clin Sci (Lond) 2022;136:197—222.

[10] Akrida I, Bravou V, Papadaki H. The deadly cross-talk between Hippo pathway and epithelial-mesenchymal transition (EMT) in cancer. Mol Biol Rep 2022;49:10065—76.

[11] Lim YX, Lin H, Seah SH, Lim YP. Reciprocal regulation of Hippo and WBP2 signalling—implications in cancer therapy. Cells 2021:10.

[12] Luo J, Yu FX. GPCR—Hippo signaling in cancer. Cells 2019;8:426. https://doi.org/10.3390/cells8050426.

[13] Yu F, Zhao B, Guan K. Hippo pathway in organ size control, tissue homeostasis, and cancer. Cell 2015;163:811—28.

[14] Calses PC, Crawford JJ, Lill JR, Dey A. Hippo pathway in cancer: aberrant regulation and therapeutic opportunities. Trends Cancer 2019;5:297—307.

[15] Meng Z, Moroishi T, Guan K. Mechanisms of Hippo pathway regulation. Genes Dev 2016;30:1—17.

[16] Ma S, Meng Z, Chen R, Guan KL. The Hippo pathway: biology and pathophysiology. Annu Rev Biochem 2019;88:577—604.

[17] Hong AW, Meng Z, Guan KL. The Hippo pathway in intestinal regeneration and disease. Nat Rev Gastroenterol Hepatol 2016;13:324—37.

[18] Ostriker AC, Martin KA. Hippo and hyperplasia. Circ Res 2019;124:1282—4.

[19] Borreguero-Muñoz N, Fletcher GC, Aguilar-Aragon M, Elbediwy A, Vincent-Mistiaen ZI, Thompson BJ. The Hippo pathway integrates PI3K—Akt signals with mechanical and polarity cues to control tissue growth. PLoS Biol 2019;17:e3000509. https://doi.org/10.1371/journal.pbio.3000509.

[20] Yu F, Zhao B, Panupinthu N, Jewell JL, Lian I, Wang LH, et al. Regulation of the Hippo—YAP pathway by G-protein-coupled receptor signaling. Cell 2012;150:780—91.

[21] Holden JK, Cunningham CN. Targeting the Hippo pathway and cancer through the TEAD family of transcription factors. Cancers 2018;10:81. https://doi.org/10.3390/cancers10030081.

[22] Huh HD, Kim DH, Jeong HS, Park HW. Regulation of TEAD transcription factors in cancer biology. Cells 2019;8:600. https://doi.org/10.3390/cells8060600.

[23] Xu J, Kausalya PJ, Ong AGM, Goh CMF, Mohamed Ali S, Hunziker W. ZO-2/Tjp2 suppresses Yap and Wwtr1/Taz-mediated hepatocyte to cholangiocyte transdifferentiation in the mouse liver. NPJ Regen Med 2022;7:55. https://doi.org/10.1038/s41536-022-00251-6.

[24] Pavel M, Park SJ, Frake RA, Son SM, Manni MM, Bento CF, et al. α-Catenin levels determine direction of YAP/TAZ response to autophagy perturbation. Nat Commun 2021;12:1703. https://doi.org/10.1038/s41467-021-21882-1.

[25] Park JA, Kwon YG. Hippo—YAP/TAZ signaling in angiogenesis. BMB Rep 2018;51:157—62.

[26] Giampietro C, Disanza A, Bravi L, Barrios-Rodiles M, Corada M, Frittoli E, et al. The actin-binding protein EPS8 binds VE-cadherin and modulates YAP localization and signaling. J Cell Biol 2015;211:1177—92.

[27] Gu Y, Wang Y, Sha Z, He C, Zhu Y, Li J, et al. Transmembrane protein KIRREL1 regulates Hippo signaling via a feedback loop and represents a therapeutic target in YAP/TAZ-active cancers. Cell Rep 2022;40:111296. https://doi.org/10.1016/j.celrep.2022.111296.

[28] Ooki T, Murata-Kamiya N, Takahashi-Kanemitsu A, Wu W, Hatakeyama M. High-molecular-weight hyaluronan is a Hippo pathway ligand directing cell density-dependent growth inhibition via PAR1b. Dev Cell 2019;49:590—604. e9. https://doi.org/10.1016/j.devcel.2019.04.018.

[29] Shalhout SZ, Yang PY, Grzelak EM, Nutsch K, Shao S, Zambaldo C, et al. YAP-dependent proliferation by a small molecule targeting annexin A2. Nat Chem Biol 2021;17:767—75.

[30] Ma B, Cheng H, Gao R, Mu C, Chen L, Wu S, et al. Zyxin—Siah2—Lats2 axis mediates cooperation between Hippo and TGF-β signalling pathways. Nat Commun 2016;7:11123. https://doi.org/10.1038/ncomms11123.

[31] Mo JS, Meng Z, Kim YC, Park HW, Hansen CG, Kim S, et al. Cellular energy stress induces AMPK-mediated regulation of YAP and the Hippo pathway. Nat Cell Biol 2015;17:500—10.

[32] Luo M, Meng Z, Moroishi T, Lin KC, Shen G, Mo F, et al. Heat stress activates YAP/TAZ to induce the heat shock transcriptome. Nat Cell Biol 2020;22:1447—59.

[33] Panda DK, Bai X, Zhang Y, Stylianesis NA, Koromilas AE, Lipman ML, et al. SCF-SKP2 E3 ubiquitin ligase links mTORC1/ER stress/ISR with YAP activation in murine renal cystogenesis. J Clin Invest 2022;132:e153943. https://doi.org/10.1172/JCI153943.

[34] Schroeder MC, Halder G. Regulation of the Hippo pathway by cell architecture and mechanical signals. Semin Cell Dev Biol 2012;23:803—11.

[35] Li Z, Chen S, Cui H, Li X, Chen D, Hao W, et al. Tenascin-C-mediated suppression of extracellular matrix adhesion force promotes entheseal new bone formation through activation of Hippo signalling in ankylosing spondylitis. Ann Rheum Dis 2021;80:891—902.

[36] Shen J, Cao B, Wang Y, Ma C, Zeng Z, Liu L, et al. Hippo component YAP promotes focal adhesion and tumour

aggressiveness via transcriptionally activating THBS1/FAK signalling in breast cancer. J Exp Clin Cancer Res 2018;37:175. https://doi.org/10.1186/s13046-018-0850-z.
[37] Claude-Taupin A, Isnard P, Bagattin A, Kuperwasser N, Roccio F, Ruscica B, et al. The AMPK—Sirtuin 1—YAP axis is regulated by fluid flow intensity and controls autophagy flux in kidney epithelial cells. Nat Commun 2023;14:8056. https://doi.org/10.1038/s41467-023-43775-1.
[38] Fernando RN, Cotter L, Perrin-Tricaud C, Berthelot J, Bartolami S, Pereira JA, et al. Optimal myelin elongation relies on YAP activation by axonal growth and inhibition by Crb3/Hippo pathway. Nat Commun 2016;7:12186. https://doi.org/10.1038/ncomms12186.
[39] Cao JJ, Zhao XM, Wang DL, Chen KH, Sheng X, Li WB, et al. YAP is overexpressed in clear cell renal cell carcinoma and its knockdown reduces cell proliferation and induces cell cycle arrest and apoptosis. Oncol Rep 2014;32:1594—600.
[40] Schütte U, Bisht S, Heukamp LC, Kebschull M, Florin A, Haarmann J, et al. Hippo signaling mediates proliferation, invasiveness, and metastatic potential of clear cell renal cell carcinoma. Transl Oncol 2014;7:309—21.
[41] Xu S, Zhang H, Chong Y, Guan B, Guo P. YAP promotes VEGFA expression and tumor angiogenesis though Gli2 in human renal cell carcinoma. Arch Med Res 2019;50:225—33.
[42] Yang WH, Ding CKC, Sun T, Rupprecht G, Lin CC, Hsu D, et al. The Hippo pathway effector TAZ regulates ferroptosis in renal cell carcinoma. Cell Rep 2019;28:2501—8. e4. https://doi.org/10.1016/j.celrep.2019.07.107.
[43] Xu T, Wei D, Yang Z, Xie S, Yan Z, Chen C, et al. ApoM suppresses kidney renal clear cell carcinoma growth and metastasis via the Hippo—YAP signaling pathway. Arch Biochem Biophys 2023;743:109642. https://doi.org/10.1016/j.abb.2023.109642.
[44] Chen X, Zhang X, Jiang Y, Zhang X, Liu M, Wang S, et al. YAP1 activation promotes epithelial—mesenchymal transition and cell survival of renal cell carcinoma cells under shear stress. Carcinogenesis 2022;43:301—10.
[45] Meng K, Hu Y, Wang D, Li Y, Shi F, Lu J, et al. EFHD1, a novel mitochondrial regulator of tumor metastasis in clear cell renal cell carcinoma. Cancer Sci 2023;114:2029—40.
[46] Xiao J, Shi Q, Li W, Mu X, Peng J, Li M, et al. ARRDC1 and ARRDC3 act as tumor suppressors in renal cell carcinoma by facilitating YAP1 degradation. Am J Cancer Res 2018;8:132—43.
[47] Kumar B, Ahmad R, Giannico GA, Zent R, Talmon GA, Harris RC, et al. Claudin-2 inhibits renal clear cell carcinoma progression by inhibiting YAP-activation. J Exp Clin Cancer Res 2021;40:77.
[48] Liu S, Yang Y, Wang W, Pan X. Long noncoding RNA *TUG1* promotes cell proliferation and migration of renal cell carcinoma via regulation of YAP. J Cell Biochem 2018;119:9694—706.
[49] Zhang W, Liu R, Zhang L, Wang C, Dong Z, Feng J, et al. Downregulation of miR-335 exhibited an oncogenic effect via promoting KDM3A/YAP1 networks in clear cell renal cell carcinoma. Cancer Gene Ther 2022;29:573—84.
[50] Wu S, He H, Huang J, Jiang S, Deng X, Huang J, et al. FMR1 is identified as an immune-related novel prognostic biomarker for renal clear cell carcinoma: a bioinformatics analysis of TAZ/YAP. Math Biosci Eng 2022;19:9295—320.
[51] Yuan N, Li G. Comprehensive analysis reveals the involvement of hsa_circ_0037858/miR-5000-3p/*FMR1* axis in malignant metastasis of clear cell renal cell carcinoma. Aging (Albany NY) 2023;15:5399—411.
[52] White SM, Avantaggiati ML, Nemazanyy I, Di Poto C, Yang Y, Pende M, et al. YAP/TAZ inhibition induces metabolic and signaling rewiring resulting in targetable vulnerabilities in *NF2*-deficient tumor cells. Dev Cell 2019;49:425—43.e9. https://doi.org/10.1016/j.devcel.2019.04.014.
[53] Zhu Z, Wei D, Xa Li, Wang F, Yan F, Xing Z, et al. RNA-binding protein QKI regulates contact inhibition via Yes-associate protein in ccRCC. Acta Biochim Biophys Sin 2019;51:9—19.
[54] Matsuura K, Nakada C, Mashio M, Narimatsu T, Yoshimoto T, Tanigawa M, et al. Downregulation of SAV1 plays a role in pathogenesis of high-grade clear cell renal cell carcinoma. BMC Cancer 2011;11:523. https://doi.org/10.1186/1471-2407-11-523.
[55] Kai T, Tsukamoto Y, Hijiya N, Tokunaga A, Nakada C, Uchida T, et al. Kidney-specific knockout of Sav1 in the mouse promotes hyperproliferation of renal tubular epithelium through suppression of the Hippo pathway. J Pathol 2016;239:97—108.
[56] Guan Y, Gong Z, Xiao T, Li Z. Knockdown of miR-572 suppresses cell proliferation and promotes apoptosis in renal cell carcinoma cells by targeting the NF2/Hippo signaling pathway. Int J Clin Exp Pathol 2018;11:5705—14.
[57] Baumgartner R, Poernbacher I, Buser N, Hafen E, Stocker H. The WW domain protein Kibra acts upstream of Hippo in Drosophila. Dev Cell 2010;18:309—16.
[58] Schelleckes K, Schmitz B, Ciarimboli G, Lenders M, Pavenstädt HJ, Herrmann E, et al. Promoter methylation inhibits expression of tumor suppressor KIBRA in human clear cell renal cell carcinoma. Clin Epigenet 2017;9:109.
[59] Miao D, Wang Q, Shi J, Lv Q, Tan D, Zhao C, et al. N6-methyladenosine-modified DBT alleviates lipid accumulation and inhibits tumor progression in clear cell renal cell carcinoma through the ANXA2/YAP axis-regulated Hippo pathway. Cancer Commun 2023;43:480—502.
[60] Yin L, Li W, Xu A, Shi H, Wang K, Yang H, et al. SH3BGRL2 inhibits growth and metastasis in clear cell renal cell carcinoma via activating Hippo/TEAD1-Twist1 pathway. EBioMedicine 2020;51:102596. https://doi.org/10.1016/j.ebiom.2019.12.005.
[61] Yu Z, Li Q, Zhang G, Lv C, Dong Q, Fu C, et al. PLEKHO1 knockdown inhibits RCC cell viability *in vitro* and *in vivo*, potentially by the Hippo and MAPK/JNK pathways. Int J Oncol 2019;55:81—92.
[62] Peng Q, Wang L, Zhao D, Lv Y, Wang H, Chen G, et al. Overexpression of FZD1 is associated with a good prognosis and resistance of sunitinib in clear cell renal cell carcinoma. J Cancer 2019;10:1237—51.
[63] Jiang Y, Zhang Y, Leung JY, Fan C, Popov KI, Su S, et al. MERTK mediated novel site Akt phosphorylation alleviates SAV1 suppression. Nat Commun 2019;10:1515. https://doi.org/10.1038/s41467-019-09233-7.
[64] Fine SW, Argani P, DeMarzo AM, Delahunt B, Sebo TJ, Reuter VE, et al. Expanding the histologic spectrum of mucinous tubular and spindle cell carcinoma of the kidney. Am J Surg Pathol 2006;30:1554—60.
[65] Reuter VE, Argani P, Zhou M, Delahunt B. Best practices recommendations in the application of immunohistochemistry in the kidney tumors: report from the International Society of Urologic Pathology consensus conference. Am J Surg Pathol 2014;38:e35—49.
[66] Mehra R, Vats P, Cieslik M, Cao X, Su F, Shukla S, et al. Biallelic alteration and dysregulation of the Hippo pathway in mucinous tubular and spindle cell carcinoma of the kidney. Cancer Discov 2016;6:1258—66.
[67] Ren Q, Wang L, Al-Ahmadie HA, Fine SW, Gopalan A, Sirintrapun SJ, et al. Distinct genomic copy number alterations distinguish mucinous tubular and spindle cell carcinoma of the kidney from papillary renal cell carcinoma with overlapping histologic features. Am J Surg Pathol 2018;42:767—77.
[68] Karakiewicz PI, Hutterer GC, Trinh QD, Pantuck AJ, Klatte T, Lam JS, et al. Unclassified renal cell carcinoma: an analysis of 85 cases. BJU Int 2007;100:802—8.

[69] Lopez-Beltran A, Kirkali Z, Montironi R, Blanca A, Algaba F, Scarpelli M, et al. Unclassified renal cell carcinoma: a report of 56 cases. BJU Int 2012;110:786—93.
[70] Crispen PL, Tabidian MR, Allmer C, Lohse CM, Breau RH, Blute ML, et al. Unclassified renal cell carcinoma: impact on survival following nephrectomy. Urology 2010;76:580—6.
[71] Sirohi D, Smith SC, Agarwal N, Maughan BL. Unclassified renal cell carcinoma: diagnostic difficulties and treatment modalities. Res Rep Urol 2018;10:205—17.
[72] Chen Y, Xu J, Skanderup AJ, Dong Y, Brannon AR, Wang L, et al. Molecular analysis of aggressive renal cell carcinoma with unclassified histology reveals distinct subsets. Nat Commun 2016;7:13131. https://doi.org/10.1038/ncomms13131.
[73] Malouf GG, Flippot R, Dong Y, Dinatale RG, Chen Y, Su X, et al. Molecular characterization of sarcomatoid clear cell renal cell carcinoma unveils new candidate oncogenic drivers. Sci Rep 2020;10:701. https://doi.org/10.1038/s41598-020-57534-5.
[74] Duong NX, Le MK, Kondo T, Mitsui T. Heterogeneity of Hippo signalling activity in different histopathologic subtypes of renal cell carcinoma. J Cell Mol Med 2023;27:66—75.
[75] Zhang B, Chu W, Wen F, Zhang L, Sun L, Hu B, et al. Dysregulation of long non-coding RNAs and mRNAs in plasma of clear cell renal cell carcinoma patients using microarray and bioinformatic analysis. Front Oncol 2020;10:559730. https://doi.org/10.3389/fonc.2020.559730.
[76] Islam MS, Afrin S, Singh B, Jayes FL, Brennan JT, Borahay MA, et al. Extracellular matrix and Hippo signaling as therapeutic targets of antifibrotic compounds for uterine fibroids. Clin Transl Med 2021;11:e475. https://doi.org/10.1002/ctm2.475.
[77] Mudianto T, Campbell KM, Webb J, Zolkind P, Skidmore ZL, Riley R, et al. Yap1 mediates trametinib resistance in head and neck squamous cell carcinomas. Clin Cancer Res 2021;27:2326—39.
[78] Barrette AM, Ronk H, Joshi T, Mussa Z, Mehrotra M, Bouras A, et al. Anti-invasive efficacy and survival benefit of the YAP-TEAD inhibitor verteporfin in preclinical glioblastoma models. Neuro Oncol 2022;24:694—707.
[79] Pancholi NJ. AACR Virtual Annual Meeting II: insights into cancer metastasis reveal potential therapeutic strategies. https://www.aacr.org/blog/2020/08/21/aacr-virtual-annual-meeting-ii-insights-into-cancer-metastasis-reveal-potential-therapeutic-strategies/. [Accessed 29 December 2023].