Advances in research on the carcinogenic mechanisms and therapeutic potential of YAP1 in bladder cancer (Review)

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Abstract. Bladder cancer is the most common malignant tumor of the urinary system with high morbidity and no clear pathogenesis. The Hippo signaling pathway is an evolutionarily conserved pathway that regulates organ size and maintains tissue homeostasis. Yes-associated protein 1 (YAP1) is a key effector of this pathway and regulates downstream target genes by binding to transcriptional co-activators with PDZ binding sequences (TAZ). Several studies have demonstrated that YAP1 is overexpressed in bladder cancer and is involved in adverse outcomes such as bladder cancer occurrence, progression, resistance to cisplatin and the recurrence of tumours. The present review summarized the involvement of YAP1 in bladder cancer disease onset and progression, and the mechanism of YAP1 involvement in bladder cancer treatment. In addition, this study further explored the potential of YAP1 in the diagnosis and treatment of bladder cancer. This study aimed to explore the potential mechanism of YAP1 in the treatment of bladder cancer.

Contents

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1. Introduction

The Hippo signaling pathway is an evolutionarily conserved signal pathway that was first identified in Drosophila and plays an important role in the regulation of cell proliferation, apoptosis and tissue and organ growth (1,2). Yes-associated protein 1 (YAP1), a pivotal component of the Hippo signaling pathway, is encoded by the YAP1 gene located on human chromosome 11q22 and functions as an oncogenic protein (Fig. 1) (3). When the Hippo pathway is disrupted, mammalian STE20-like protein kinase 1/2 (Mst1/2) kinases become phosphorylated and activated, which in turn activates downstream large tumor suppressor kinase 1 and 2 ((LATS1/2) kinases. These activated LATS1/2 kinases phosphorylate YAP1, leading to its degradation in the cytoplasm (4). Conversely, dephosphorylated YAP1 translocates to the nucleus, binds to the TEA domain (TEAD) and promotes the transcription of downstream genes (for example, CTGF and Cyr61) (5,6).

YAP1/transcriptional co-activator with PDZ-binding motif (TAZ) play essential roles in regulating cell proliferation and are crucial for organ regeneration, development and stem cell self-renewal (7). They are influenced by various factors, including the microenvironment and extracellular signals. Additionally, YAP1 can activate survival pathways to inhibit apoptosis and interacts with multiple signaling networks (8), contributing to cancer development and progression (9). Elevated YAP1 expression is associated with malignant tumor recurrence, metastasis, reduced overall survival and chemotherapy resistance (10). In human cancers, YAP/TAZ target genes are associated with poor prognosis and increased treatment resistance (11). YAP1 is highly expressed in various cancers and linked to adverse outcomes, including bladder, colon, pancreatic, hepatocellular, gastric/esophageal, ovarian, brain, breast and lung cancers (12-17).

Bladder cancer is the most prevalent malignancy within the urinary system and is anticipated to rank as the ninth most common cancer in the United States by 2023 (18). Previous years have seen an increasing incidence of bladder cancer, with a trend toward younger patients (19). While the etiology remains incompletely understood, risk factors include smoking, aging and occupational exposures (20). Genetic mutations and altered RNA expression levels also contribute to bladder cancer risk. YAP1 is notably upregulated in bladder cancer and is associated with poor prognosis (21). Research indicates that single

nucleotide polymorphisms (SNPs) in YAP1, a key molecule in the Hippo pathway, are linked to bladder cancer development (22). BCa is a cancer that frequently exhibits mutations. A study has indicated that in human bladder smooth muscle, Gene Ontology annotation analysis shows that differential genes are enriched in positive regulation of cellular processes, metabolism, protein binding and signal transduction processes. Kyoto Encyclopedia of Genes and Genomes enrichment analysis highlights genes in the MAPK and PI3K/Akt signaling pathways (23). Additionally, a next-generation sequencing study suggests that BCa is primarily associated with a high mutation burden in genes related to the cell cycle and chromatin regulation. Dysfunctional Hippo signaling may contribute to the development of bladder cancer, although it is not an independent driver (24). The present study reviews the carcinogenic mechanisms of YAP1 in bladder cancer and evaluates its potential as a therapeutic target.

2. Regulation of YAP1 activity in bladder cancer

YAP1 activity is controlled by its gene expression levels. Knockdown of this gene in bladder cancer cell lines significantly reduces YAP1 protein activity (21). Furthermore, the primary method of regulating YAP1 activity involves modulation of its phosphorylation status. When phosphorylated, YAP1 is retained in the cytoplasm and thus is unable to translocate to the nucleus to perform its transcriptional activation functions. 4-hydroxynonenal induces phosphorylation of YAP1 at serine residues 127 and 387, leading to reduced YAP1 expression and consequently decreases bladder cancer cell proliferation (25). Ubiquitination is regulated by deubiquitinases (DUBs), which are specialized Ub proteases that process Ub chains in various ways to regulate ubiquitination (26). MINDY1, a DUB specific to YAP1, removes the K48-linked ubiquitin chain from YAP1, thereby preventing its proteasomal degradation. This action enhances the stability and abundance of the YAP1 protein, consequently boosting its transcriptional activation capability and facilitating the progression of bladder cancer (Fig. 2) (27).

3. YAP1 participates in the progression of bladder cancer

Tumor cell proliferation and migration is a dynamic and intricate process that contributes to the advancement of numerous diseases. Abnormal cell proliferation often leads to tumor formation. Once tumor cells acquire the capability to migrate and detach from the primary site, they can significantly accelerate tumor dissemination and metastasis. Phosphorylated YAP1 not only directly influences tumor proliferation but also collaborates with various molecules to promote both tumor proliferation and migration. For instance, The drosophile Mask (multiple ankyrin repeats single KH domain) whose mammalian homologues MASK1 (also known as ANKHD1) and MASK2 (also known as GTAR or ANKRD17) are a novel cofactor of YAP1. In bladder cancer cell lines overexpressing YAP1, MASK2interacts with YAP1 to modulate its downstream target genes, consequently promoting the proliferation and migration of bladder cancer cells (28).

The MAPK pathway, ubiquitously present in organisms, potentially facilitates the onset and progression of cancer when its signaling becomes dysregulated (29). YAP1 serves as both an upstream regulator and an activator of the MAPK pathway. Its stimulation of the MAPK/ERK pathway synergistically promotes the proliferation and invasion of bladder cancer cells (30). Research demonstrates that YAP1 modulates the transcription of both long non-coding RNA (lncRNA) and mRNA (31). Specifically, lncRNA H19, a downstream target of YAP1, is upregulated by YAP1, influencing the proliferation and migration of bladder cancer cells (32). Furthermore, in bladder cancer, lncRNA H19 interacts with microRNA (miRNA/miR)-29b-3p, impacting epithelial-mesenchymal transition (EMT) and thereby facilitating cancer metastasis (33).

Furthermore, YAP1 can collaborate synergistically with miRNA to facilitate the progression of bladder cancer. MiRNAs, serving as critical regulatory factors in tumor development, are intricately linked to tumor formation, metastasis, cellular apoptosis and chemoresistance when expressed abnormally (34). A study by Luo (35) identified a cross-network interaction between the Hippo and TGF-β signaling pathways, where the YAP1-Smad3 complex plays a pivotal role. MiR-497 and miR-195 disrupt the formation of the YAP1/SMAD3 complex, thereby interfering with the interactions between the Hippo/YAP1 and TGF-β/Smad pathways. This disruption diminishes their influence on the shared target gene, connective tissue growth factor (CTGF), ultimately reducing bladder cancer cell proliferation (36). Furthermore, the overexpression of hypermethylated in cancer 1 suppresses CTGF activity, limits interactions between YAP1 and the TEAD, and inhibits proliferation, migration and invasion of bladder cancer cells (37). Additionally, miR-599 curtails proliferation and invasion, while enhancing apoptosis in bladder urothelial carcinoma cells by modulating YAP1 expression (38).

Exosomes, a type of extracellular vesicle, are secreted by virtually all cell types. These vesicles support a wide array of cellular functions, encompassing intercellular communication, cell differentiation and proliferation, angiogenesis, stress responses and immune signaling (39,40). Research demonstrates a distinct relationship between exosomes and YAP1, where exosomal miR-217 from normal human bladder stromal cells is significantly elevated in bladder cancer cell lines, and by modulating YAP1 and its downstream targets, cysteine-rich angiogenic inducer 61 (CYR61), CTGF and ankyrin repeat domain-containing protein 1 miR-217 mimics or inhibitors can notably influence the proliferation, migration, and apoptosis of bladder cancer cells (41).

EMT is a critical process in tumor metastasis and a hallmark of malignant tumors. Additionally, EMT is integral to embryogenesis and wound healing (42,43). In a study, high-glucose culture media induces YAP1 and TAZ expression in bladder cancer cells, resulting in the upregulation of wave protein, N-cadherin, and fibronectin, alongside the downregulation of E-cadherin to promote EMT, while also regulating glucose metabolism through glucose transporter type 1 activity, thereby highlighting the Hippo signaling pathway as a crucial factor in the dysregulation of glucose metabolism in bladder cancer (Table I) (44).

Stem cells (SCs) are multipotent cells with the capacity for self-renewal. Provided specific conditions, these cells can differentiate into a variety of functional cell types (45,46). Cancer SCs (CSCs) are characterized by their capacity for self-renewal and differentiation. These cells significantly

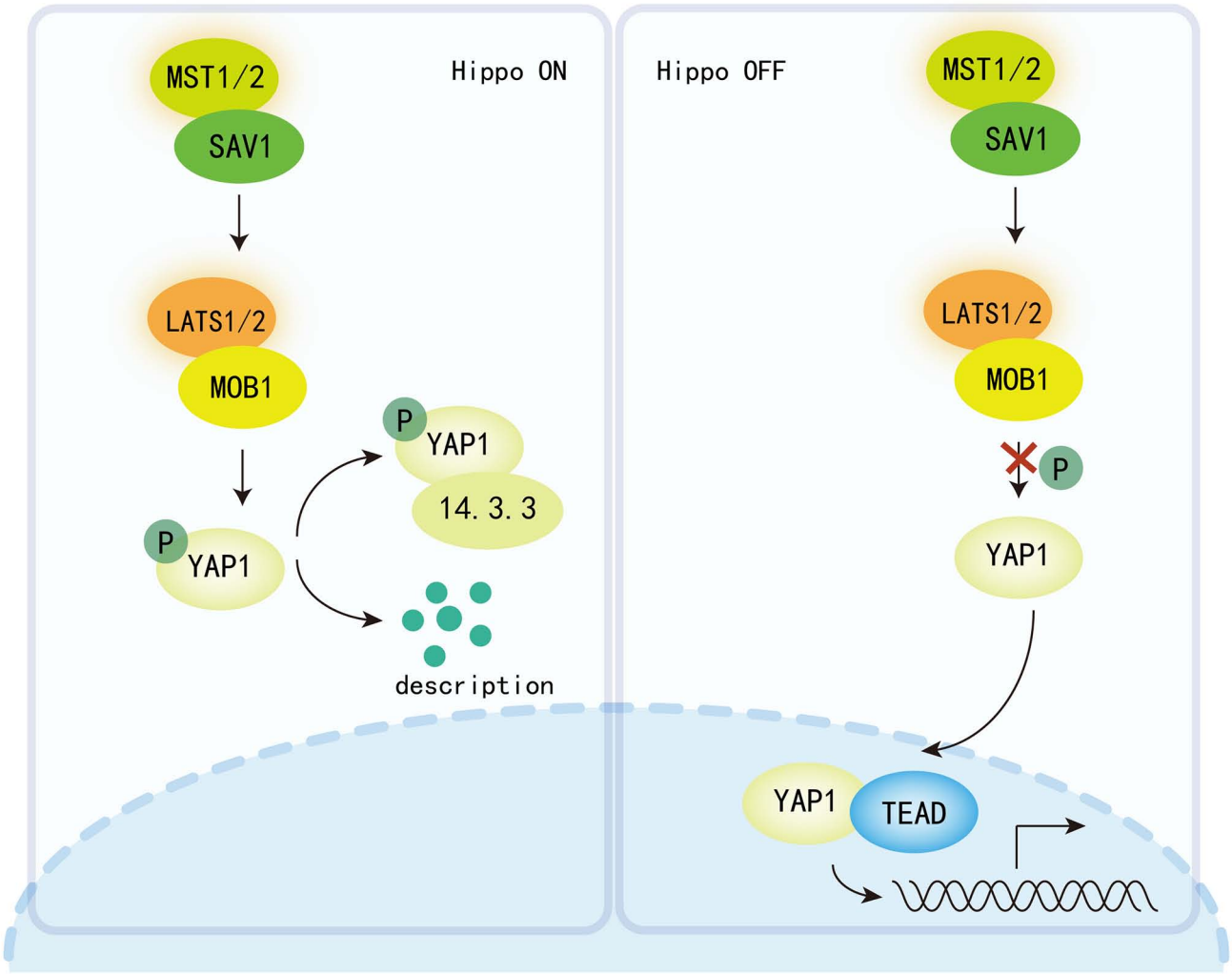

Figure 1. Hippo signaling pathway is a key regulator of cellular and systemic metabolism, maintaining organ size and tissue homeostasis by controlling cell proliferation, survival and regeneration. When the Hippo signaling pathway is activated (in the 'ON' state), MST1/2 kinases phosphorylate LATS1/2, which in turn promotes the phosphorylation of YAP/TAZ. This leads to the retention of YAP/TAZ in the cytoplasm and/or their degradation via the proteasome pathway, thereby inhibiting their transcriptional co-activator activity. Conversely, when the Hippo signaling pathway is inactivated (in the 'OFF' state), dephosphorylated YAP/TAZ can freely translocate to the nucleus, where they bind to the TEAD family of transcription factors and activate the expression of a range of genes involved in cell growth, proliferation, and survival. MST, macrophage-stimulating; LATS1/2, large tumor suppressor kinase 1/2; YAP, Yes-associated protein; TAZ, transcriptional co-activator with PDZ-binding motif; TEAD, TEA domain; SAV1, Salvador family WW domain-containing protein 1; MOB1, MOB kinase activator 1; P, phosphorylated.

contribute to tumor progression, treatment resistance and disease recurrence by continuously proliferating, invading normal tissues and exhibiting resistance to conventional cancer therapies (47,48).

YAP1 is pivotal in regulating several key processes in CSCs, including self-renewal, multilineage differentiation, tumorigenesis, treatment resistance and metastatic invasion (49,50). In embryonic, neural and hematopoietic stem cells, elevated expression of the YAP1-TEAD2 complex sustains stem cell potency and serves as an indicator of stemness (51). YAP1, a regulator of stem cell functions, is notably upregulated in bladder cancer stem cells. The overexpression of YAP significantly enhances the self-renewal ability of these cells (52). YAP1 collaborates with the pro-inflammatory cyclooxygenase 2 (COX2)/prostaglandin E2 (PGE2) signaling pathway to enhance the proliferation of bladder urothelial carcinoma stem-like cells and influence tumor chemoresistance. As the COX2/PGE2 pathway induces methylation of the let-7 promoter, this results in reduced let-7 expression and subsequent upregulation of SRY-box transcription factor 2 (SOX2), which is further amplified by YAP1's binding to the SOX2 enhancer, thereby increasing SOX2 expression (53). The interaction between the COX2 and YAP1 pathways may significantly influence the recurrence of bladder cancer.

Furthermore, the miR-146a rs2910164 SNP genotype C>G significantly affects the prognosis of bladder cancer patients by modulating key targets within the Hippo and COX2 signaling pathways, leading to the suppression of YAP1 and COX2 at both mRNA and protein levels, which results in the downregulation of YAP1 and aldehyde dehydrogenase 1 family, member A1, along with reduced expression of COX2 and SOX2, all of which are closely associated with bladder cancer recurrence (54). Simultaneously, a study has demonstrated that YAP1 is involved in its own recurrence process. During the postoperative wound healing phase in bladder cancer, it has been observed that the extracellular matrix regulates the

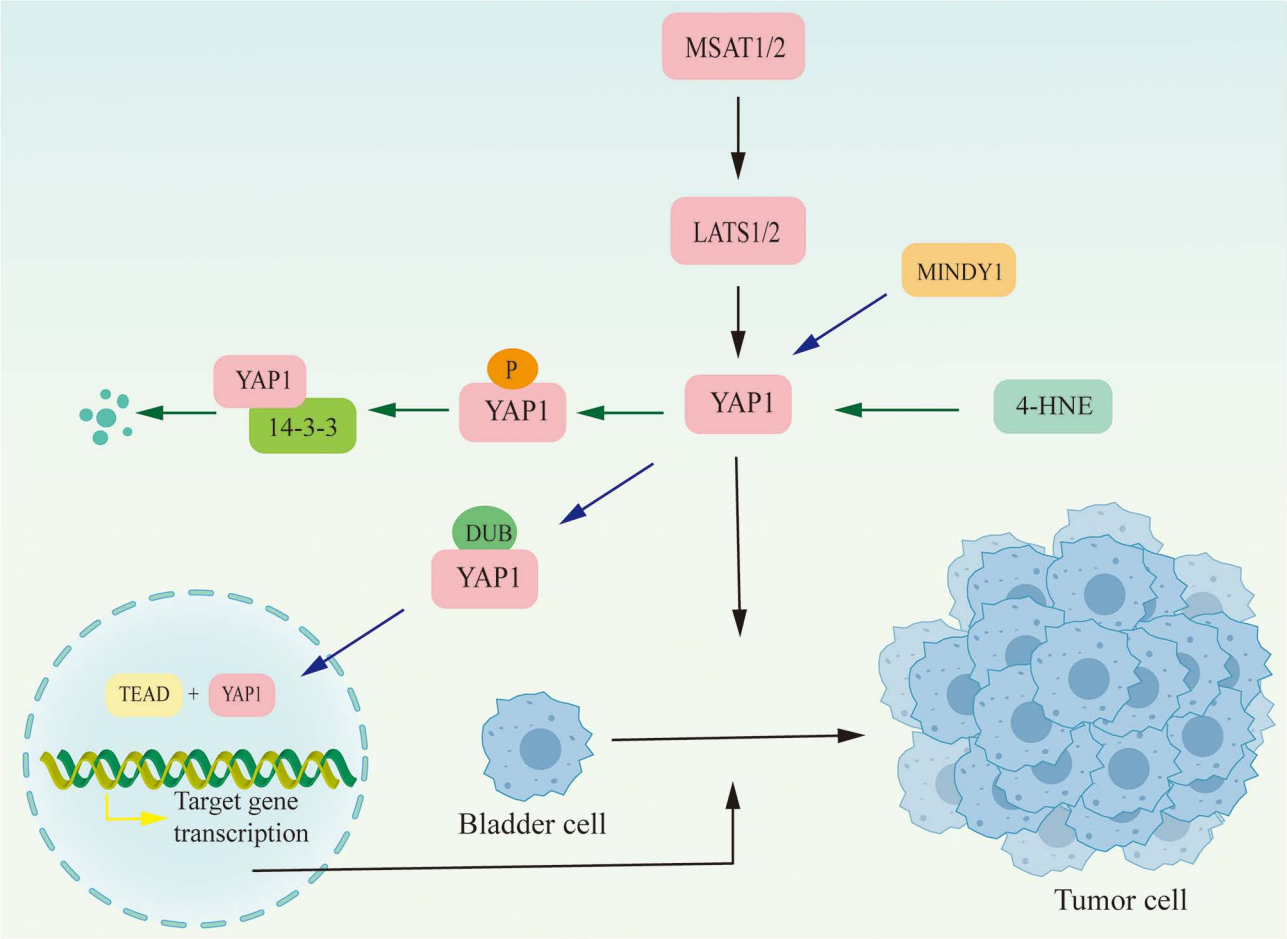

Figure 2. In bladder cancer, YAP1 activity is regulated by YAP1 gene expression, post-transcriptional mRNA modifications, and the activity of the Hippo signaling pathway. YAP1 protein modifications also affect its activity and function. 4-HNE regulates YAP1 activity through phosphorylation, accelerating its degradation, while MINDY enhances its stability through deubiquitination. Activated YAP1 will enter the nucleus and bind to TEAD to regulate downstream target genes. 4-HNE, 4-hydroxynonenal; YAP, Yes-associated protein; LATS1/2, large tumor suppressor kinase 1/2; DUB, deubiquitination; TEAD, TEA domain.

transport of YAP1 to the nucleus through integrin-FAK-YAP1 signaling. This regulation contributes to the progression and recurrence of bladder cancer (55).

This implies that YAP1 overexpression not only affects bladder cancer progression through interactions with multiple signaling pathways but also contributes to this progression by regulating the stemness of tumor stem cells. Consequently, targeting YAP1 and its associated regulatory network could provide novel therapeutic approaches for bladder cancer.

4. Therapeutic potential of YAP1-targeting in bladder cancer

Bladder urothelial carcinoma is classified into two main categories based on clinical staging, each with different clinical outcomes and treatment options: Muscle invasive bladder cancer (MIBC) and non-MIBC (NMIBC). Treatment decisions are primarily based on clinical factors. Besides surgery, common treatments currently include cisplatin chemotherapy, immunotherapy and targeted therapy. Despite these options, the treatment outlook for bladder cancer remains unsatisfactory, with a high risk of recurrence. Although the targeting of cancer treatment signaling pathways has increased over the past few decades, bladder cancer requires the exploration of potentially more effective treatments (Table II).

YAP1 and chemotherapy resistance in bladder cancer. Chemotherapy remains a cornerstone of treatment for malignant tumors, with cisplatin used across a spectrum of cancers, including bladder cancer (56-58). Yet, the emergence of cisplatin resistance has notably diminished its therapeutic effectiveness (59,60). Moreover, the redox state, crucial in the adaptation of cancer cells to therapeutic stresses, significantly influences chemoresistance (61). Research demonstrates that YAP1 activation plays a pivotal role in conferring resistance across targeted therapy, chemotherapy, radiotherapy and possibly immunotherapy, thus establishing it as a critical mediator of chemoresistance in diverse cancers (62,63).

The YAP1/TEAD complex is known to regulate Forkhead box protein M1(FOXM1) expression, which in turn affects nuclear factor erythroid 2-related factor 2 (Nrf2) expression (64). Both Nrf2 and YAP1 contribute to the antioxidative capacity of bladder cancer cells, with a positive association observed between the expression levels of YAP1 and Nrf2. Targeted inhibition of YAP1 and Nrf2, aimed at decreasing cell viability, inducing apoptosis and curbing cancer cell

Table I. In bladder cancer cell lines, YAP1 and its downstream signaling pathways influence various biological behaviors of bladder cancer.

Signaling network	Major outcomes	Cell line used/ bladder subtype	(Refs.)
YAP1/Mask2	Overexpression of YAP1 can promote the growth and migration of bladder cancer cells. The YAP1/Mask2 complex controls the growth and migration of bladder cancer cells by regulating the expression of target genes in the Hippo pathway.	5637	(28)
YAP1/MAPK	YAP1 overexpression activates proteins and their phosphorylated forms in the MAPK pathway, including ERK, p38 and JNK, thereby enhancing the cellular proliferative capacity and invasiveness of bladder cancer cells.	5637/UMUC-3/J82	(30)
YAP1/H19	YAP1 expression is significantly upregulated in bladder cancer and facilitates cancer cell proliferation and migration by increasing the expression of the long non-coding RNA H19.	5637/UMUC-3	(32)
YAP1/TGF-β/Smad	MiRNAs miR-497 and miR-195 inhibit the expression and interaction of YAP1 and Smad3, thereby diminishing the activity of the YAP1-Smad3 complex and consequently suppressing the progression of bladder cancer.	5637/T24	(36)
HIC1/YAP1	Overexpression of HIC1 reduces the binding of YAP1 to TEAD, inhibits the activity of the YAP1/TEAD pathway, and thereby suppresses the progression of bladder cancer.	J28/T24	(37)
YAP1/COX2/PGE2	YAP1 and the COX2/PGE2 signaling pathway synergistically activate SOX2, thereby promoting cancer stem cell properties and enhancing chemotherapy resistance.	BFTC905/BFTC909/ 5637/T24	(53)

In multiple bladder cancer cell lines, YAP1 is integrated into signaling networks, influencing the progression of bladder cancer. Specifically, YAP1 interacts with signaling pathways such as Mask2 and MAPK, and collaborates with H19 and HIC1. HIC1, hypermethylated in cancer 1; COX2, cyclooxygenase 2; YAP, Yes-associated protein; PGE2, prostaglandin E2.

migration, has been shown to substantially enhance the sensitivity of these cells to cisplatin (66). The transcription factor Nrf2 is a pivotal regulator of antioxidant defenses and cellular protection mechanisms, playing a significant role in mediating cisplatin resistance in bladder cancer (66). Emerging research based on the interaction between YAP1 and Nrf2 indicates that Ailanthone (Aila) can potentially serve as an effective therapeutic for cisplatin-resistant bladder cancer. Notably, Aila consistently suppresses Nrf2 expression while concurrently inhibiting YAP1 and c-Myc, thereby sustaining a robust anti-proliferative effect on cisplatin-resistant cells (67). Additionally, Aila markedly decreases the expression of the Nrf2 target glutathione S-transferase A4 and the YAP1/TEAD target survivin. In cisplatin-resistant bladder cancer cells, levels of intracellular oxidative stress are notably lower compared with those in cisplatin-sensitive cells. The post-translational downregulation of Nrf2 and YAP1 proteins can effectively reduce cancer cell proliferation and migration, while simultaneously increasing oxidative stress in chemotherapy-resistant bladder cancer cell lines (68). Decitabine, a DNA methyltransferase inhibitor, demonstrates cytotoxic effects at high doses by directly inducing cell death. At lower doses, it reactivates silenced genes via demethylation of promoter regions and is extensively employed in the treatment of diseases such as leukemia (69).

In bladder cancer cells, decitabine reactivates the Hippo signaling pathway through the restoration of Ras association domain-containing protein 1, concurrently inhibiting YAP1 expression and reducing the expression of its oncogenic downstream targets, including CTGF and CYR61. Furthermore, decitabine enhances the cytotoxic effects of cisplatin and doxorubicin in these cells (70). YAP1 expression and activation are inversely correlated with cisplatin sensitivity both *in vitro* and *in vivo*. The YAP1 inhibitor verteporfin has been demonstrated to inhibit tumor cell proliferation and enhance cisplatin sensitivity in bladder cancer cells. Inhibition of YAP1 expression increases DNA damage and promotes apoptosis accumulation, thereby sensitizing urothelial carcinoma cells to radiochemotherapy. Notably, nuclear YAP1 expression is linked to adverse outcomes in patients with urothelial

Table II. Main mechanism and mode of action of YAP1 in the treatment of bladder cancer.

Treatment method	Mechanism of action	Functions	(Refs.)
Chemotherapy: Resistance	YAP1 contributes to chemoresistance and antioxidant response in bladder cancer cells by regulating the expression of Nrf2 and FOXM1 and modulating intracellular oxidative stress levels.	YAP1 maintains cellular antioxidant status by regulating the intracellular antioxidant system, specifically through the modulation of GSH synthesis and utilization.	(65)
	YAP1 increases the chemoresistance of bladder urothelial carcinoma cells to drugs such as cisplatin by inhibiting apoptosis and promoting cell survival signaling pathways.	Activation of YAP1 decreases cellular sensitivity to DNA-damaging drugs and inhibits the apoptotic pathway by reducing the activation of apoptosis-related proteins caspase 3 and PARP induced by chemotherapy.	(71)
Immunotherapy	Knockdown of YAP1 reduces cell invasiveness and migratory ability, likely due to the involvement of YAP1-regulated genes such as CTGF and CYR61, which play crucial roles in extracellular matrix remodeling and cell migration.	YAP1 plays a critical role in the proliferation, colony formation, invasiveness and migratory ability of bladder cancer cells by regulating multiple molecules and signaling pathways involved in cell cycle progression, migration, invasion and gene expression.	(80)
Molecular Targeted Therapy:	Verteporfin inhibits bladder cancer cell growth and invasion by suppressing the expression of downstream genes in the Hippo signaling pathway activated by YAP1.	The function of YAP1 is inhibited, which in turn suppresses the expression of target genes in the Hippo signaling pathway, thereby inhibiting the growth and invasion of bladder cancer cells.	(85)

Knocking down YAP1 can inhibit chemoresistance in bladder cancer. YAP1 may also serve as a biomarker for bladder cancer immunotherapy. Additionally, the YAP1-targeting drug VP inhibits the proliferation and migration of bladder cancer cells. CRY61, cysteine-rich angiogenic inducer 61; YAP1, Yes-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; FOXM1, forkhead box M1; GSH, glutathione; CTGF, connective tissue growth factor.

carcinoma undergoing perioperative chemotherapy (71). The YAP1/TEAD1/PDGF-BB/PDGFR autocrine loop plays a pivotal role in sustaining the characteristics of tumor stem-like cells. Inhibition of YAP1 has been shown to significantly reduce cisplatin resistance in OV6-positive bladder cancer stem-like cells, a finding corroborated by animal model studies.

YAP1 and bladder cancer immunotherapy. Immunotherapy is a treatment method aimed at enhancing the body's immune system or modifying the ongoing cancer defense mechanisms to combat cancer (72,73). In recent years, immunotherapy has gained prominence in cancer treatment and has undergone rapid development (74). In bladder cancer, Bacillus Calmette-Guérin (BCG) remains the preferred immunotherapy for NMIBC, effectively stimulating immune responses and modulating the immune system to produce antitumor effects, thereby significantly reducing recurrence rates and prolonging the interval between recurrences (75,76). Nevertheless, ~1/3 of patients with NMIBC do not respond to BCG therapy. A previous study indicates that combining programmed cell death protein 1 (PD-1) inhibitors with BCG treatment is a safe and potentially effective strategy for these non-responders (77). Additionally, immune checkpoint inhibitors (ICIs) such as PD-1 and programmed death-ligand 1 (PD-L1) antibodies are approved for bladder cancer treatment. These ICIs can directly interact with the urothelium or malignant cells on the bladder mucosa, initiating active immune responses (78). Baek *et al* (79) revealed three molecular subtypes of advanced urothelial carcinoma through gene expression analysis, which have potential clinical application value in predicting responses to immune checkpoint inhibitor therapy and patient prognosis. Among these, the inactivation of the YAP/TAZ pathway in the third subtype is associated with the activation of cell cycle and DNA damage response pathways. This suggests that in patients with the third subtype, the inactivation of the YAP/TAZ pathway might be related to a good response to ICI therapy and improved prognosis (79). Further research by Baek *et al* (80) categorized YAP1 activation into three distinct subtypes based on differential gene expression and integrated this classification with immunotherapy prognostic analysis for patients. This analysis suggests that NMIBC subgroups with YAP1 activation might derive significant benefit from ICI treatments. Additionally, the activation status of YAP1 in NMIBC is not only associated with the biological behavior of the disease but also has the potential to serve as a crucial biomarker for predicting treatment response and patient prognosis (80).

YAP1 and targeted therapy for bladder cancer. Based on platinum-based chemotherapy, which serves as the first-line treatment for patients with NMIBC, survival rates are improved

but still remain relatively low (81). Advances in targeted therapies, which have transformed treatment paradigms in various cancers, are only beginning to make inroads into bladder cancer (82,83). Approved treatments such as PD-1/PD-L1 inhibitors, the fibroblast growth factor receptor inhibitor Erdafitinib, and Enfortumab vedotin (an antibody-drug conjugate directed at Nectin-4 that comprises a fully human, monoclonal antibody and the microtubule-disrupting agent, monomethyl auristatin E) have shown promise (84). Notably, Enfortumab vedotin has achieved a remission rate of ~8% in patients with locally advanced or metastatic bladder cancer previously treated with platinum-based and anti-PD-1/PD-L1 therapies (85). Furthermore, the YAP1-specific inhibitor, Verteporfin (VP), demonstrates potential as a targeted therapeutic by inhibiting YAP1-induced gene expression within the Hippo pathway and reducing the proliferation and invasion of bladder cancer cells in a dose-dependent manner (86). Dual treatment involving Crizotinib and VP in canine bladder cancer organoids significantly reduce cell vitality by inducing apoptosis, underscoring the potential of combining Crizotinib with VP (87). An additional study has explored the synergistic effects of Verteporfin and the RhoA inhibitor Simvastatin, which counteract the proliferative and metastatic activities induced by PLAGL2. Protein kinase membrane-associated tyrosine/threonine 1, another direct target of YAP1/TEAD1, is implicated in activating the YAP1/TAZ pathway, further highlighting the complex regulatory mechanisms in bladder cancer pathogenesis (88).

5. Limitations and prospects

YAP1, recognized as an oncogene (89), plays critical roles in cell proliferation, migration, epithelial-mesenchymal transition, stemness and chemotherapy resistance across various malignancies, including bladder cancer. However, research on YAP1 in bladder cancer mainly focuses on bladder transitional cell carcinoma, and there is a lack of exploration regarding the expression and mechanisms of YAP1 in other subtypes of bladder cancer (such as bladder squamous cell carcinoma, bladder adenocarcinoma and bladder sarcoma). Despite its established significance in the molecular mechanisms underlying bladder cancer, *in vivo* experimental validation remains limited, and the regulatory mechanisms of the upstream factors of YAP1 are poorly understood. Enhanced exploration of the HIPPO signaling pathway's interactions in bladder cancer could revolutionize diagnostic and therapeutic approaches. Currently, post-translational modifications of YAP1 are extensively studied in various human solid tumors (90-92). Ubiquitination modification of YAP1 has been confirmed to be of significant importance for tumor progression in multiple tumors (14,93).

Additionally, glycosylation modification of YAP1 can increase its stability, promoting the malignant development of chronic kidney disease (94). Previous research findings suggest that metabolic pathways play a role in regulating YAP/TAZ activity. Glycolysis, energy stress and mevalonate biosynthesis have been identified as regulators of YAP/TAZ activity (95). Currently, glucose metabolism is a hotspot in tumor research. At present, metabolic diagnostics can improve accuracy and affordability (96). YAP1 is also involved in the tumor glycolysis process and is considered a glucose metabolism regulator. YAP1 mediates cardiac hypertrophy induced by pressure overload through aerobic glycolysis (97). In thyroid tumors and liver tumors, high glucose levels regulate YAP1 activity and promote tumor progression (98,99). In bladder tumors, research has shown that extracellular glucose levels regulate YAP1 and promote the progression of bladder cancer EMT (44). In bladder cancer, YAP1 is not only related to glucose metabolism but also acts as an oncogene and glycoprotein, making it a promising tumor marker for bladder cancer. Currently, research combines composite materials with metabolic analysis to screen for potential biomarkers (100). YAP1 is expected to become a biomarker in bladder cancer; however, extensive clinical data is still needed to clarify the sensitivity and specificity of YAP1.

YAP1, known as a cancer stem cell marker, contributes to the progression of bladder cancer. However, while a previous study has examined YAP1's interactions with other molecular pathways affecting cancer stem cell dynamics, the exact mechanisms of YAP1's involvement in these processes remain poorly defined (49). Research indicates that YAP1/TAZ may be a new decisive factor in ferroptosis (101). Activation of ferroptosis can specifically target and kill certain cancer cells, leading to improved survival rates. Ferroptosis is currently a major focus in tumor research. Meanwhile, a single study suggests that nanomaterials and copper ions could offer new approaches for tumor treatment (102). However, there are currently no reports on the interaction between YAP1 and ferroptosis in bladder cancer.

Although YAP1-targeted inhibitors have demonstrated efficacy in various cancers, research specifically addressing these inhibitors in bladder cancer is sparse, and their molecular mechanisms of action are not well understood. Additionally, YAP1 expression is closely linked to the occurrence, size and stage of bladder cancer, highlighting its potential as a biomarker. Despite the high recurrence rate of bladder cancer, research into the fundamental mechanisms driving this recurrence is inadequate. Notably, the expression of YAP1 is associated with recurrence rates, but detailed investigations into how YAP1 contributes to bladder cancer recurrence are still required.

6. Conclusion

In summary, there is a critical need for comprehensive studies in bladder cancer focusing on several key areas: i) The interactions of the Hippo signaling pathway with YAP1, particularly its post-translational modifications and their impact on tumor progression; ii) the dynamics between YAP1 and glucose metabolism; iii) the role of YAP1 in bladder cancer stem cell behavior; iv) the effectiveness of YAP1-targeted inhibitors in clinical treatment; and v) the specific mechanisms through which YAP1 contributes to bladder cancer recurrence. Given its significant influence on various cancer-related processes, YAP1 holds great promise as a novel biomarker and therapeutic target for bladder cancer.

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Authors' contributions

TH contributed to the creation of figures, drafted the manuscript and conducted research. LF contributed to table creation and drafted the manuscript. JT contributed to revision of the manuscript. SC contributed to drafting the original manuscript. GD contributed to drafting manuscript. ZN contributed to the conceptual design, provided resources, oversaw the project and reviewed and edited the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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