

REVIEW ARTICLE

The potential relationship between YAP and PCNP in esophageal carcinoma and its influence on carcinogenesis

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Abstract

Esophageal cancer is one of the malignant tumors with high incidence and mortality rates worldwide. Its occurrence and development involve abnormal regulation of multiple signaling pathways. In recent years, the role of Hippo signaling and PEST-containing nuclear protein (PCNP) in esophageal cancer has gradually received attention. As a key regulator of organ size and tissue homeostasis, the Hippo pathway exerts its biological effects primarily through its core effector Yes-associated protein (YAP)/TAZ; accumulating evidence confirms that aberrant activation of YAP is closely linked to esophageal cancer occurrence, progression, lymph node metastasis, and chemoresistance, making it a critical oncogenic driver. PCNP, a highly conserved nuclear protein, together with its E3 enzyme NIF, is involved in modulating cell cycle progression, DNA damage repair, and apoptotic signaling under physiological conditions. However, its overexpression in esophageal cancer tissues has been associated with accelerated tumor growth and unfavorable patient outcomes, potentially through interactions with downstream oncogenic mediators such as NIF2. This review summarizes the research progress on the Hippo pathway and PCNP, and proposes a possible mechanistic interplay between them in esophageal cancer based on their functions, focusing on exploring their mechanisms of action, regulatory relationships, and potential therapeutic targets in the occurrence and development of esophageal cancer, in order to provide ideas for diagnosis, prognosis, and targeted therapy of esophageal cancer.

Keywords: Hippo pathway; PEST-containing nuclear protein; Esophageal cancer; YAP/TAZ; Targeted therapy

1. Introduction

Esophageal cancer is a common cancer of the digestive tract, with about 300,000 people dying from esophageal cancer worldwide each year, and the 5-year survival rate is about 15% to 25%.^{1,2} The incidence and mortality rates vary greatly among countries, depending on climatic conditions and dietary habits.³ In China, esophageal cancer accounts for 11% of deaths caused by cancer, ranking seventh in the *Chinese Cancer Bulletin*, with an average of about 150,000 deaths every year. Smoking, drinking, and unhealthy dietary habits are the three major risk factors.^{1,3-5} Esophageal cancer is mainly categorized into two histopathological types: Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Squamous dysplasia is the prodromal lesion of ESCC, whereas Barrett's esophagus is a precancerous lesion that precedes the development of EAC.

Smoking and excessive alcohol consumption are universally recognized as the most prominent risk factors for esophageal cancer, because long-term exposure to these habits can significantly elevate the likelihood of malignant transformation in the esophageal epithelium.^{6,7} Besides these primary triggers, multiple factors contribute to the incidence of this disease, including unhealthy dietary patterns (*e.g.*, frequent intake of pickled, spicy, or scalded foods), chronic gastroesophageal reflux disease, Barrett's esophagus, obesity, and inherited genetic susceptibilities. At the molecular level, esophageal cancer pathogenesis is closely linked to dysregulated signaling pathways: overexpression of epidermal growth factor receptor (EGFR) amplifies pro-proliferative and survival signals, whereas abnormal activation of the cyclin D-CDK4/6 complex disrupts cell cycle checkpoints, driving uncontrolled cell division and malignant proliferation.^{8,9}

In clinical practice, traditional treatments like endoscopic resection are limited by poor long-term prognosis and frequent adverse reactions in many cases. Currently, chemoradiotherapy (CRT) serves as a core therapeutic modality, primarily used for locally advanced disease, unresectable tumors, or palliative care to alleviate symptoms (*e.g.*, dysphagia) and extend survival.¹⁰ Targeted therapy, valued for its precision and mild side effects, benefits advanced patients with specific molecular targets. For instance, HER2-targeted tyrosine kinase inhibitors improve survival in esophageal-gastric adenocarcinoma. Programmed death-1 (PD-1) immunotherapy is another effective option for advanced esophageal cancer, working by blocking the PD-1 pathway to restore the anti-tumor activity of T cells against cancer cells.^{11,12} At present,

targeted therapy has also become a therapy option for esophageal cancer. The Hippo pathway involved in YAP affects the occurrence and development of esophageal cancer. Therefore, we speculate that YAP is related to the pathogenesis of esophageal cancer, and it is speculated that targeted YAP may also become a method for the treatment of esophageal cancer.

The Hippo signaling pathway was first uncovered in *Drosophila melanogaster* around 20 years ago, with initial studies highlighting its central role in governing organ growth and preventing hyperplasia during developmental processes. Over the past two decades, research spanning model organisms and human tissues has underscored the pathway's evolutionary conservation and broadened its recognized functions, encompassing the regulation of tissue homeostasis, stem cell self-renewal, and the restraint of unregulated cell division (key processes that act as barriers against tumor formation). YAP serves as the primary downstream effector of the Hippo pathway, functioning as a transcriptional co-activator that translates upstream signals into cellular responses. Under physiological conditions, the Hippo pathway maintains strict control over YAP activity through a well-orchestrated kinase cascade: upstream components, including MST1/2 kinases and their adaptor protein SAV1, initiate signaling by phosphorylating and activating LATS1/2 kinases. These activated LATS1/2 then directly phosphorylate YAP, triggering its sequestration in the cytoplasm and targeting it for degradation via the ubiquitin-proteasome pathway. This regulatory mechanism effectively limits YAP's nuclear translocation and transcriptional activity under normal circumstances. Notably, perturbations in this cascade, which lead to the YAP dephosphorylation, nuclear accumulation, and persistent activation, have been implicated in the pathogenesis of various cancers, including esophageal cancer, where YAP acts as a critical oncogenic mediator to drive cell proliferation, evade apoptosis, and augment the invasive and metastatic potential of tumor cells.¹³⁻¹⁵ In recent years, the role of YAP in esophageal cancer has also been widely studied. In esophageal cancer, inactivation of the Hippo signaling pathway may lead to abnormal activation of YAP, which promotes the occurrence and development of esophageal cancer by affecting its mitosis, cell adhesion, and apoptosis.¹⁶

PEST-containing nuclear protein (PCNP) is a conserved nuclear protein (NP) characterized by a PEST sequence, and this motif is closely associated with protein degradation and turnover. As a nucleus-localized factor, PCNP exerts multifaceted roles in regulating fundamental biological processes, including gene transcription modulation, DNA damage repair cascades,

and cell cycle progression (key events that maintain cellular homeostasis under physiological conditions). Emerging evidence suggests that PCNP is dysregulated in esophageal cancer, where its aberrant expression may disrupt normal cellular dynamics and contribute to tumorigenesis. Notably, accumulating studies imply that PCNP might interact with YAP, the core effector of the Hippo signaling pathway, to modulate esophageal cancer development.¹⁷

In this review, we systematically review the current research progress on the roles of YAP and PCNP in esophageal cancer. We summarize YAP's well-established oncogenic functions, such as promoting cell proliferation, inhibiting apoptosis, and enhancing invasion, as well as PCNP's emerging role in regulating tumor-related signaling networks. Furthermore, we hypothesize that YAP and PCNP may share intrinsic functional links or engage in direct/indirect interactions, synergistically driving the initiation, progression, and metastasis of esophageal cancer. This review aims to shed light on their potential crosstalk and lay a foundation for exploring novel diagnostic biomarkers and targeted therapeutic strategies.

2. Hippo signaling pathway and YAP/TAZ

2.1. Hippo pathway is involved in regulating organ size

The Hippo pathway was first discovered in *Drosophila*, which controls cell growth, proliferation, and differentiation, and plays an important role in organ growth and development. The mammalian Hippo pathway consists of several key components, including mammalian STE20-like kinase1/2 (MST1/2), protein Salvador homologue 1 (SAV1), and MOBKL1A/B (MOB1A/B), large tumor suppressor kinase 1/2 (LATS1/2), YAP, WW-domain-containing transcription regulator 1 (TAZ), and transcriptional enhanced associate domain (TEAD) family.^{18,19} Under normal physiological conditions, when cells contact with each other, MST1/2 is activated and continues to phosphorylate the LATS1/2 kinase complex. Activated LATS1/2 phosphorylates downstream YAP/TAZ to prevent it from entering the nucleus and binding to TEAD for transcription. Phosphorylated YAP/TAZ is trapped in the cytoplasm to be eventually degraded. Thus, the Hippo pathway is in charge of maintaining the growth and development of normal cells²⁰⁻²² (Figure 1).

2.2. Phosphorylated YAP/TAZ remains in the cytoplasm to control cell growth

YAP/TAZ is a transcriptional co-activator of Hippo signaling, located downstream of this pathway, and it is translocated between the nucleus and cytoplasm, playing

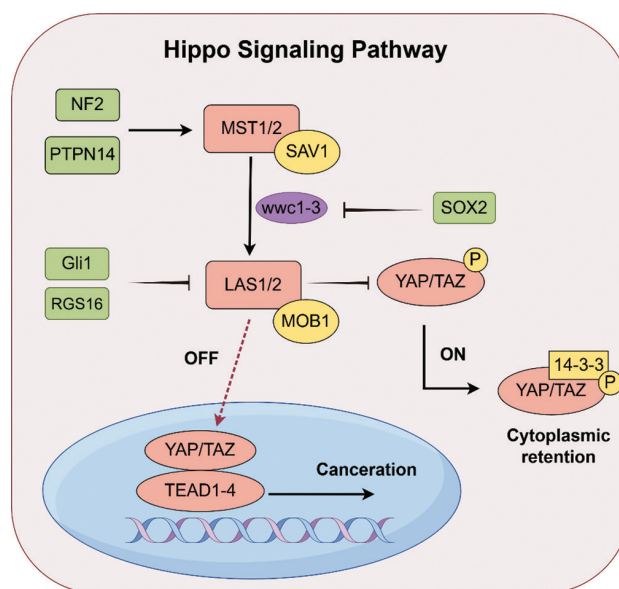


Figure 1. Core components of the mammalian Hippo pathway. MST1/2, LATS1/2, YAP/TAZ, and TEAD1-4 are the core components of the Hippo pathway, and the localization of YAP/TAZ in cells determines the activation and deactivation of the Hippo pathway. Under physiological conditions, YAP/TAZ is phosphorylated by LATS1/2 kinase and degraded by 14-3-3 proteins in the cytoplasm, leaving the pathway activated. In a pathological state, YAP/TAZ enters the nucleus and binds to TEAD to initiate the transcription of pro-proliferative genes, leaving the pathway deactivated. Image created using Figdraw by the authors. Abbreviation: YAP: Yes-associated protein.

a role in controlling cell and organ growth.²³ Under physiological conditions, YAP is phosphorylated by LATS1/2, binds to 14-3-3 proteins, obscures its nuclear localization signal, and is retained in the cytoplasm, thereby inhibiting cell proliferation and promoting cell apoptosis.²⁴ Under pathological conditions, Hippo signaling is inactivated, thus YAP enters the nucleus, binds to TEAD to form a transcription complex, enhances the transcription activity of the TEAD family, and regulates downstream signals, to accelerate cell proliferation and survival, thereby facilitating the occurrence and progression of cancers/tumors^{25,26} (Figure 1). In addition, YAP1 can act as an inhibitor of TAZ expression in esophageal cancer through transcriptional and translational functions.¹⁶ At present, studies have shown that YAP/TAZ is abnormally expressed in many diseases, and as a new target to guide the treatment of diabetes, YAP/TAZ is also used as a prognostic indicator for patients.²⁷⁻²⁹

2.3. Functions of the Hippo pathway

Since its initial discovery, the Hippo signaling pathway has become a focal point of biomedical research, with investigations expanding from its foundational role in developmental biology to its multifaceted implications

in cancer pathogenesis. Beyond governing organ size and tissue homeostasis, recent studies have uncovered its involvement in diverse physiological and pathological processes, including organ development and tumor progression. For example, the pregnane X receptor (PXR) has been shown to facilitate the binding of YAP to TEAD transcription factors, whereas peroxisome proliferator-activated receptors (PPARs, also classified as NR1C) interact with the YAP–TEAD complex to drive hepatomegaly, highlighting the pathway's role in liver overgrowth.^{30,31}

In cardiac development, the Hippo pathway exerts precise regulatory control: interactions between YAP or β -catenin with transcription factors such as Snai2 or Sox2 have been observed, revealing that Hippo signaling and canonical Wnt pathways function antagonistically to constrain cardiomyocyte proliferation, thereby maintaining the heart's normal size and function.³² Accumulating evidence across malignancies further confirms the Hippo pathway's critical role in modulating cell proliferation, migration, and apoptosis in human cancers. In breast cancer, the leukemia inhibitory factor receptor acts as an upstream regulator of Hippo signaling, suppressing metastasis and serving as a valuable prognostic biomarker.²⁹ In colorectal cancer, YAP restricts the nuclear translocation of Dishevelled during regenerative growth, thereby inhibiting Wnt signaling and constraining tumor progression.³³ These cross-tissue and cancer-specific findings underscore the Hippo pathway's evolutionarily conserved and context-dependent functions, laying the groundwork for exploring its crosstalk with PCNP in esophageal cancer.

2.4. Implications of the Hippo pathway in esophageal cancer

The Hippo pathway is prevalent in human malignancies, as well as in esophageal cancer.³⁴ It is often disrupted in esophageal cancer, inducing cancer cells to proliferate and migrate, thereby manifesting cancer characteristics (Figure 2). For instance, regulators of G-protein signaling (RGS) constitute a family of proteins that negatively regulate G-protein-mediated signaling. In esophageal cancer, RGS16 disrupts the interaction between Ste20-like kinases 1 (MST1) and LATS1. The phosphorylation levels of LATS1 and YAP were decreased, thus activating YAP in the ESCC nucleus and enhancing the invasion and migration of ESCC.³⁵ The aberrant activation of glioma-associated oncogene homolog 1 (Gli1) is observed in esophageal cancer cells. When abnormally activated, Gli1 upregulates YAP1 in a LATS1-independent manner, and in turn, YAP1 upregulates Gli1 through the regulation of PI3K/AKT signaling.³⁶ These pathological changes

enhance the manifestation of ESCC cellular features. Sox is a transcription factor, and its HMG-box domain, associated with Sry, mediates its binding with DNA to affect cell growth and organ development.³⁷ In esophageal cancer, Sox2 inhibits WWC1 drive in the Hippo pathway, thereby inhibiting the activation of YAP1 and reducing the phenotype of ESCC.³⁸ Sox9 fully binds to the promoter of TEAD, which, after regulation by YAP1, upregulates Sox9, to exhibit tumor characteristics.^{39,40} These studies all suggest that the Hippo pathway plays an important role in esophageal cancer, and disruption of the Hippo pathway will cause cells to express cancer cell characteristics.

3. Regulation of YAP/TAZ and YAP/TAZ-mediated regulation

3.1. Regulation of YAP/TAZ by microRNA

MicroRNAs are single-stranded RNAs encoded by endogenous genes that are involved in the regulation of post-transcriptional gene expression and tumor cell invasion and metastasis.⁴¹ miR-34a-5p targets lymphoid enhancer-binding factor 1 (LEF1) and inhibits Hippo–YAP1/TAZ signaling, thereby inhibiting the proliferation, migration, and invasion of ESCC.⁴² In addition, microRNAs can also target YAP1 to enhance cancer cell resistance to cisplatin and paclitaxel.^{43–45} miR-624 targets arrestin domain-containing 3 (ARRDC3) to decrease its expression, increase YAP expression, activate the hypoxia-inducible factor-1 α (HIF1 α) signaling, and enhance ESCC resistance.⁴⁴ The expression of miR-141 is upregulated in cisplatin-resistant esophageal cancer cells, which directly target the 3'-untranslated region of YAP1. As is known, miR-141 plays a key role in DNA damage-induced apoptosis, and it can downregulate the expression of YAP1 to contribute to cisplatin-resistant ESCC.^{43,46}

3.2. Mitosis and YAP

RING finger-domain 1 (RNF106), a member of the RING ubiquitin ligase family, plays an indispensable role in regulating cell mitosis and migration (core processes governing cellular homeostasis and tumor progression). Beyond its canonical functions, RNF106 is involved in cell cycle modulation by prolonging the G0/G1 phase of cell division, thereby influencing the timing of cell proliferation. Emerging research in esophageal cancer has revealed a functional link between RNF106 and YAP1: knockdown of RNF106 significantly enhances YAP1 phosphorylation, a modification that promotes YAP1 cytoplasmic retention and degradation, ultimately suppressing tumor cell proliferation.⁴⁷

In addition, cyclin-dependent kinase 6 (CDK6), a key regulator of cell cycle progression through the G1/S transition, has been found to be amplified in esophageal

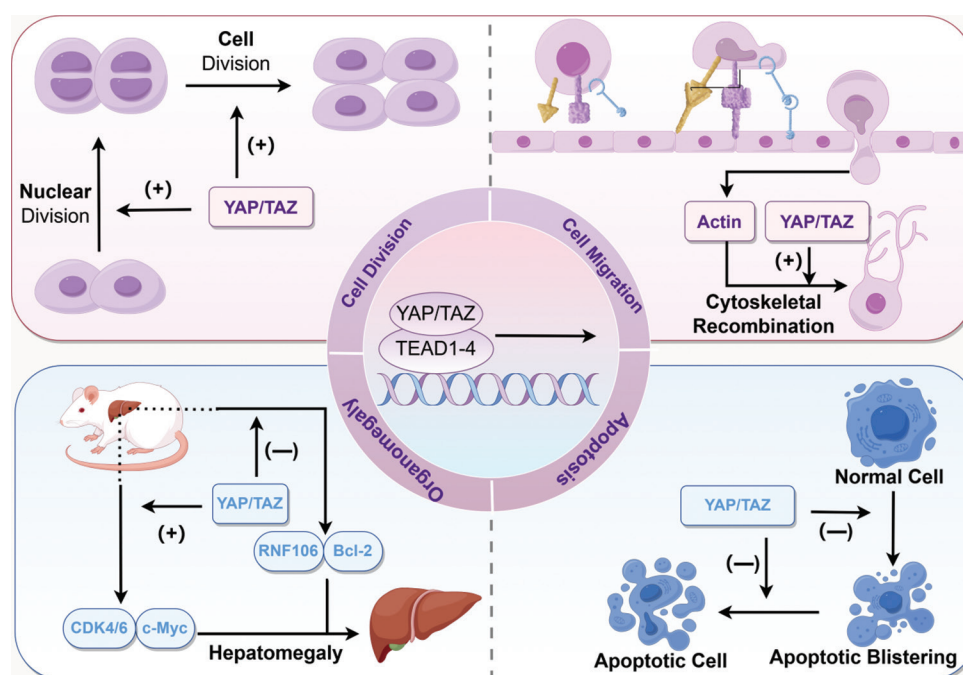


Figure 2. Dysregulation of the Hippo pathway in cells and organs. Dysfunctional Hippo pathway shortens the mitotic duration, accelerates the process of cell division, promotes cell migration, inhibits cell apoptosis, and ultimately promotes the growth of organs by regulating cell cycle factors. Image created using Figdraw by the authors.

cancer, which is positively correlated with YAP1 levels. Treatment with LEE001, a selective CDK4/6 inhibitor, effectively downregulates YAP1 expression in esophageal cancer cells, induces G1 phase cell cycle arrest, and reduces the proportion of cells in the S phase. Collectively, these findings demonstrate that YAP1 tightly regulates cell cycle progression and mitosis in esophageal cancer. Targeting upstream regulators such as RNF106 via inhibiting CDK4/6 with small-molecule agents such as LEE001 can attenuate YAP1-driven oncogenic activity, offering promising strategies to inhibit cancer cell growth and proliferation.⁴⁸

3.3. Cell adherence and YAP

YAP, a central effector of the Hippo signaling pathway, exerts profound regulatory effects on cytoskeletal tension and dynamics (key determinants of cell shape, adhesion, and motility). Beyond this, YAP drives tumor cell migration and angiogenesis—two interconnected processes critical for metastatic spread—collectively underscoring its pivotal role in mediating esophageal cancer cell adhesion and invasive capacity.⁴⁹

FAT1, a transmembrane member of the cadherin superfamily, functions as a key modulator of tumor cell adhesion and migration. In esophageal cancer models, FAT1 has been shown to upregulate the expression of protein tyrosine phosphatase nonreceptor type 14 (PTPN14) while concurrently downregulating YAP and

the oncogenic transcription factor Myc. These findings imply that FAT1 likely modulates esophageal cancer cell proliferation, adhesion, and migration through its regulatory control over PTPN14, YAP, and Myc levels.⁵⁰

Further validating YAP's functional importance, treatment with verteporfin, a selective YAP inhibitor, effectively suppresses proliferation, adhesion, and angiogenesis in ESCC cells.⁵¹ Together, these observations reinforce YAP as a core mediator of aggressive esophageal cancer phenotypes, while identifying FAT1 as a potential upstream regulator of YAP activity, laying the groundwork for exploring interactions between these pathways and PCNP in tumor progression.

3.4. Cell apoptosis induced by YAP/TAZ

YAP/TAZ orchestrates the expression of a broad array of apoptosis-related genes, thereby exerting pivotal roles in shaping cancer pathogenesis by balancing cell survival and death. Their regulatory functions in apoptosis have been well-documented across various malignancies, with context-dependent effects. In hepatocellular carcinoma, TAZ interacts with the multifunctional transcription factor c-Myc and modulates Hippo pathway activity, ultimately inducing apoptotic cell death and constraining tumor development.⁵² In non-small cell lung cancer, YAP exerts pro-apoptotic effects by suppressing Bcl-2—modifying factor induction, an event that otherwise enables cancer

cells to escape apoptosis, and can also enhance tumor cell apoptosis when combined with photodynamic therapy.^{53,54}

In esophageal cancer, accumulating evidence highlights YAP1's critical involvement in apoptotic regulation: elevated expression of miR-195 directly inhibits YAP1, leading to suppressed cell proliferation and enhanced apoptosis. In addition, the histone demethylase JMJD1C controls EAC progression by regulating H3K9me2 activity and specifically targets YAP1 to promote apoptotic signaling, thereby inhibiting tumor development. Collectively, these cross-tumor and esophageal cancer-specific studies underscore YAP1's multifaceted and central role in modulating apoptosis.^{55,56} Given this functional importance, targeting YAP1-mediated apoptotic pathways holds substantial promise as a novel breakthrough for developing innovative therapeutic strategies against esophageal cancer.

4. PEST-NPs and their functions/regulation

4.1. PEST proteolytic signal containing an NP with its characteristics

NPs are complexes formed by the non-covalent binding of proteins and nucleic acids (DNA or RNA), which are widely distributed in eukaryotic and prokaryotic cells and play core roles in nucleic acid metabolism and cellular life activities. Evidence has proven that NPs are implicated in various cell biological processes through ubiquitination, including repairing and condensing genomic content, cell division, stem cell generation, and maintaining cellular structure.⁵⁷⁻⁶⁰ Among these NPs, PEST-proteins (PEST-NPs) exert key roles predominantly via their inherent PEST motifs. PEST motifs contain acidic residues glutamate, the hydroxylated amino acids serine, aspartate, proline, and threonine. This motif serves as a critical molecular signal that triggers the rapid destruction of target proteins via intracellular proteolytic pathways such as the ubiquitin-proteasome system, which mediates the selective degradation of short-lived or misfolded proteins. Notably, the PEST motif itself can be efficiently identified and detected through the utilization of PEST-FIND, a specialized computer-based algorithm and bioinformatics tool that is specifically designed to scan and indicate the presence, location and potential functional relevance of PEST motifs within given amino acid sequences by leveraging predefined sequence patterns and scoring matrices optimized for recognizing the characteristic residue composition and structural features of these degradation-signaling elements.⁶¹ This class of PEST-NPs is considered a protector of the cell and is believed to directly participate in the hexosamine biosynthetic pathways, glycosylation of nuclear pores, and the ubiquitin-proteasome pathway.^{62,63} In addition, some of the PEST-NPs are also involved in regulating cancer

metabolism by interfering with key signaling pathways and cancer-immune mechanisms through autophagy or apoptosis.⁶⁴ In this section, we focus on two PEST-NPs: PCNP (PEST proteolytic signal-containing NP) and NIRF (Np95/ICBP90-like RING finger protein).

4.2. PCNP is implicated in various biological processes

PCNP was discovered in data mining back in 2002, when researchers discovered a novel PEST-containing protein and named it "PCNP." It is a specific protein made by one or more proline (P), threonine (T), serine (S), and glutamic acid (E) existing in the PEST motif.⁶⁵⁻⁶⁷ PCNP can induce rapid degradation of target proteins through ubiquitylation, which enables it to transfer across the nuclear membrane, involving various cellular processes, such as cell cycle, DNA repair, protein transport, and differentiation; alternatively, PCNP-mediated protein degradation occurs with concentration changes induced by alterations in the activation level of signaling pathways triggered by tumors or cancers.¹⁷ For instance, the expression level of PCNP in nervous system cancer/tumor was obviously higher than that in healthy tissues. Current studies suggest that PCNP is able to interact with cell cycle regulators, including tumor suppressors (*e.g.*, retinoblastoma protein, pRB, and p53) and promoters (*e.g.*, cyclin D and cyclin E), to regulate either apoptosis or cell proliferation. PCNP levels tend to be variable in different types of cancer/tumors, which can be the result of these mechanisms. First, in certain malignant tumors, PCNP overexpression may promote cell proliferation and inhibit apoptosis, contributing to tumor growth and invasiveness. Second, abnormal activation of upstream signaling pathways in specific cancer types can drive transcriptional upregulation of the *PCNP* gene, leading to increased protein levels. In addition, PCNP elevation may correlate with poor tumor differentiation or advanced clinical stages, serving as a potential indicator of aggressive tumor behavior.^{68,69}

4.3. NIRF functions as a regulator of the cell cycle

As a cell proliferation-associated protein, NIRF shows a specific domain configuration, including a RING finger, a PHD finger, a YDG/SRA domain, and an ubiquitin-like domain.⁷⁰⁻⁷² Owing to its specific amino acid sequences and conserved structural domains, NIRF is endowed with the molecular basis to exert multiple biological functions. Among these, a key role lies in its involvement in cell cycle regulation and DNA integrity maintenance, processes that are critical for preserving genomic stability and preventing aberrant cell proliferation.^{65,71,72} Normally, the mammalian cell cycle is a highly conserved process, which is controlled by the activities of cyclin-dependent kinases (CDKs).

Cyclins interact with CDK1 or CDK2 in a cycle-dependent manner to control cell cycle regulatory processes.⁷³ Ub is a highly conserved protein across all species, containing only 76 amino acids. The main driver of the progression of the cell cycle is the activation of CDKs, in order partly regulated via the Ub-mediated proteolysis of their kinase inhibitors (CKIs) and cyclin partners.⁷⁴ In various types of tumors, the *NIRF* gene is located at the site responsible for chromosomal DNA amplification. It interacts indirectly or directly with cyclin or CDKs to fine-tune the transition between G1, S, G2, and M phases, ensuring that cells proceed through the cycle in a controlled manner, and it shows abnormal expression (elevated or decreased), indicating that *NIRF* is involved in cell cycle regulation and tumorigenesis in certain types of human tumors.⁷⁵⁻⁷⁷ *NIRF* serves as a ubiquitin ligase to regulate the cell cycle through the ubiquitin process of cyclins.⁶⁵ As an NP, PCNP should structurally be regulated by *NIRF*, and recent literature reports have verified this,⁶⁵ leading to the postulation that PCNP communicates with *NIRF* like other suppressors/promoters in the signaling pathway of cell cycle regulation.

4.4. PCNP is a multifunctional protein

In the dynamic structure of eukaryotic cells, protein complexes are in a constant state of assembly and disassembly to drive cellular signal transduction; meanwhile, proteins continuously shuttle between different subcellular compartments, thereby completing various biological processes. PCNP shuttles through the membrane of the nucleus and regulates the tumor cell cycle through ubiquitination with the existence of *NIRF* (Figure 3). Its ubiquitination plays an important role in the activation of transcription factors, especially through interactions with STATs. PCNP co-localization with *NIRF* in the nucleus may induce apoptosis by directly interacting with DNA.^{78,79} PCNP participates in chromatin-mediated transcriptional regulation to affect the transcriptional activation or inhibition of specific target genes and multiple oncogenes, including STATs and NF- κ B, and also regulates apoptosis index through TRIF-dependent PI3K signaling, thereby affecting cell apoptosis and survival.^{68,80}

5. Implications of PCNP in esophageal cancer and other cancers/tumors

5.1. Transcriptional regulation via PCNP

Excessive supply or hyperactivation of transcription factors mediated by NPs underlie the uncontrolled growth and metastatic behavior observed in all human cancers. These transcription factors are characterized by short lifespans, enrichment in PEST sequences, and regulation through proteolysis (primarily via ubiquitin-mediated degradation).

Besides, there is a more direct interaction between PCNP and β -catenin, and this interaction is positively correlated with ovarian cancer. Co-immunoprecipitation (Co-IP) assays have confirmed that PCNP can directly interact with β -catenin to prevent it from being recognized by the degradation complex; after binding to β -catenin, PCNP significantly extends the protein half-life of β -catenin, reduces its ubiquitin-mediated degradation, and promotes its translocation into the nucleus, thereby increasing the nuclear β -catenin content, and the nuclear-accumulated β -catenin further activates the Wnt/ β -catenin signaling pathway and enhances the transcriptional activity of downstream target genes in the pathway, with analysis from the GEPIA database revealing a positive correlation between PCNP and the genes that activate this pathway.⁸¹ In addition, the Wnt/ β -catenin signaling pathway exerts direct control over the nuclear localization and transcriptional activity of Hippo YAP/TAZ by regulating the assembly and disassembly of the β -catenin destruction complex. Notably, these two pathways exhibit a spatiotemporal co-expression pattern during zebrafish embryonic development, and their regulatory relationship is characterized by consistency as well as tissue specificity during embryonic development.⁸² Since the β -catenin pathway exists in ESCC, previous studies have shown that changes in upstream factors of Wnt/ β -catenin can have an impact on the proliferation of EAC cells, and PCNP might also be a possible target in both of these esophageal cancers.^{83,84}

5.2. Cell proliferation and apoptosis regulated by PCNP

The PI3K/Akt/mTOR cascade, whose phosphorylation sites (Tyr458/Tyr199, Ser473, and Ser2448) are key residues for the activation of PI3K, AKT, and mTOR proteins, and changes in their phosphorylation levels directly reflect the activation status of the pathway, results in biological processes of cancer, including cell survival, motility, metabolism, genomic instability, angiogenesis and inflammatory cell recruitment,⁸⁵⁻⁸⁷ and has been considered a widely therapeutic target for cancer treatment. Several investigations suggest that overexpression of PCNP reduces the level of PI3K/AKT/mTOR signaling by controlling its phosphorylation level in multiple types of cancer cells.^{68,80} However, its effects on cancer cells differ in various types of cancer. In lung cancer and colon cancer, high level of PCNP reduces cell apoptosis and enhance autophagy by upregulating the phosphorylation levels of STAT3 and STAT5 along with PI3K/Akt/mTOR signaling to promote cell proliferation, migration, and invasion, while PCNP knockdown showed the opposite trend. In neuroblastoma, results are contrary.⁶⁸ Although

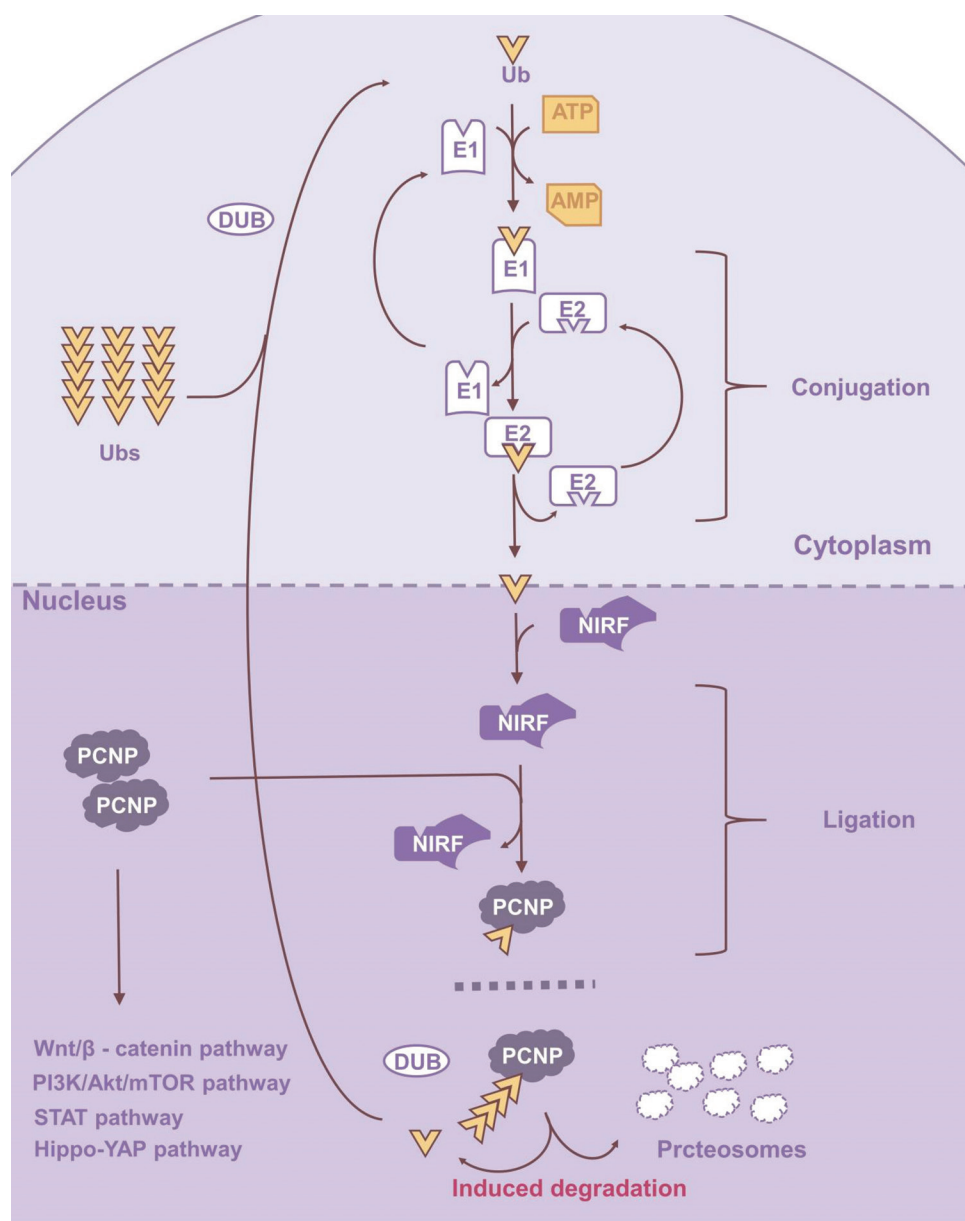


Figure 3. Ubiquitination regulation of PCNP. Ubiquitylated PCNP degenerates into proteasomes, which regulate other pathways.¹⁷ Image created using Figdraw by the authors.

Abbreviation: PCNP: PEST-containing nuclear protein.

phosphorylation levels of PI3K/Akt/mTOR signaling are established, caspase-3 could inactivate PARP due to the ratio change of the Bcl-2 family, eventually resulting in the apoptotic cascade. PCNP overexpression can remarkably raise the apoptotic index: cleaved caspase level and Bax/Bcl-2 ratio, suggesting the activation of the mitochondria-mediated pathway. Thus, PCNP knockdown can greatly decrease the level of apoptosis, suggesting that PCNP has a pro-apoptotic function in human neuroblastoma.^{23,68,79,80} It has been reported that the PI3K/AKT/mTOR pathway is activated in esophageal cancer, and p-mTOR is positively

correlated with tumor staging or grading.⁸⁸ PCNP exerts a bidirectional regulatory effect on this signaling cascade: overexpression of PCNP inhibits PI3K/AKT/mTOR pathway activation by phosphorylation, thereby promoting apoptosis and exerting an anti-tumor effect, whereas PCNP knockdown enhances pathway activation to facilitate vessel and tissue, thereby indirectly accelerating cell proliferation and migration, consequently exerting a pro-tumor effect. Importantly, this regulatory role of PCNP has been well validated in neuroblastoma models.^{59,79} Therefore, it is logical to speculate that PCNP might influence esophageal

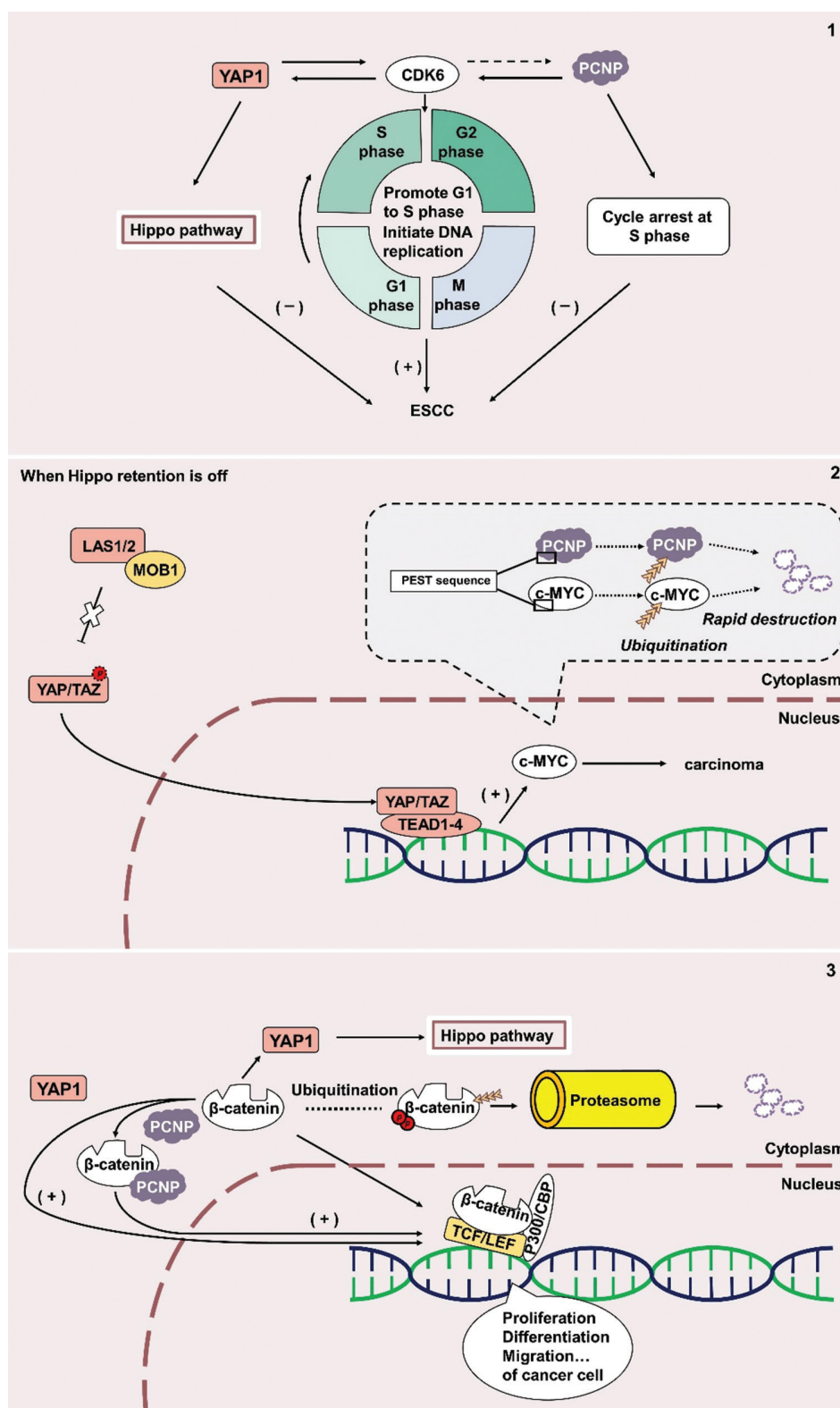


Figure 4. Possible regulatory relationship between PCNP and YAP in esophageal cancer. These three hypotheses regarding the possible regulatory relationship between PCNP and YAP will provide novel insights into the diagnosis, treatment, and prognosis evaluation of esophageal cancer. Image created using Figdraw by the authors.

Abbreviations: PCNP: PEST-containing nuclear protein; YAP: Yes-associated protein.

cancer via the PI3K/Akt/mTOR pathway. To confirm its validity, experimental studies in esophageal cancer models are required to identify the role of PCNP in apoptosis regulation via PI3K/Akt/mTOR and to establish tumor-specific evidence of its regulatory mechanisms. Compared to normal tissues, EAC tissues present decreased levels of pro-apoptotic factors (Bad, Bak, and Bax) and increased levels of anti-apoptotic factors (Bcl-2 and Bcl-xL). In addition, subsequent findings suggest that some medicine (epinodosin) inhibits the viability, invasion, and migration of ESCC cells and induces apoptosis by mediating miRNA-143-3p and eventually through the Bcl-2 ratio, significantly reducing the growth of ESCC.^{89,90} Therefore, it is logical to speculate that PCNP might have the potential to influence the growth of esophageal cancer through tuning the apoptotic index.

6. Conclusion and future directions

According to the current literature, both YAP and PCNP are highly expressed in esophageal cancer tissues, but whether they are intrinsically related is not clear. With existing evidence, we have envisaged some reasonable hypotheses. It was found that CDK6 was positively correlated with YAP1 expression in esophageal cancer, which regulates the cell cycle and affects mitosis in esophageal cancer. PCNP regulates the cell cycle process, possibly by affecting the expression and activity of CDKs, which indicates that PCNP may affect the growth of esophageal cancer cells by affecting the expression of the CDK family and regulating YAP1⁹¹⁻⁹³ (Figure 4).

c-Myc, an important transcription factor, is an essential regulator of cell proliferation, differentiation, and apoptosis. In the Hippo pathway, inactivation of the Hippo cascade promotes Myc-driven hepatocarcinoma, and the PEST sequence of c-Myc is associated with its rapid degradation, ensuring its transient expression in cells. This suggests that the PEST sequence may control the degradation of c-Myc, further regulate TAZ, and affect cellular transcription. Therefore, targeting c-Myc and TAZ may provide an approach to treating esophageal cancer^{52,94,95} (Figure 4).

In PCNP-overexpressing cells, the half-life of β -catenin was significantly prolonged, enabling activation of the Wnt/ β -catenin signaling pathway.⁹⁶ Experiments on zebrafish embryos demonstrated that the Wnt/ β -catenin signaling had a positive regulatory effect on YAP/TAZ activity. Therefore, PCNP may accelerate the expression and activation of YAP by regulating the Wnt/ β -catenin signaling to influence the occurrence of esophageal cancer^{81,82} (Figure 4).

In summary, the current evidence supports three plausible hypotheses regarding the potential intrinsic

link between YAP and PCNP in esophageal cancer. First, PCNP may indirectly regulate YAP1 by modulating the expression and activity of the CDK family, leveraging the established positive correlation between CDK6 and YAP1 in the regulation of esophageal cancer cell cycle and mitosis. Second, the PEST sequence, shared by PCNP and c-Myc, implies a potential cross-regulatory network, where PCNP might influence c-Myc degradation, further impacting TAZ activity and downstream transcriptional events relevant to the Hippo pathway. Third, PCNP could promote YAP expression and activation by stabilizing β -catenin, thereby activating the Wnt/ β -catenin signaling pathway that positively regulates YAP/TAZ function. These hypothesized mechanisms collectively highlight the multi-dimensional crosstalk between PCNP and YAP, shedding light on their synergistic role in esophageal cancer carcinogenesis. Clarifying these interactions through future experimental validation will not only deepen our understanding of the disease's molecular pathogenesis but also provide novel targets for the development of precise diagnostic and therapeutic strategies for esophageal cancer.

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Conflict of interest

Xinying Ji is an Associate Editor, whereas Yang An serves as a member of the Youth Editorial Board of this journal, but they were not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Availability of data

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