A study on the biological processes involved in YAP/TAZ and its role in intestinal disease

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Abstract

YAP/TAZ are two homologous transcriptional coactivators that promote cell proliferation, stem cell maintenance, and tissue homeostasis. Activated YAP/TAZ reflects the “social” behavior of cells, including cell adhesion and mechanical signals that cells receive from tissue structures and the surrounding extracellular matrix (ECM). Simultaneous activation or overexpression of YAP/TAZ has been shown to lead to cellular transformation and tumor development. Intestinal diseases are mostly inflammatory and tumor-based, and YAP/TAZ plays an important role in this process. However, many roles of the YAP/TAZ in the course of intestinal disease are not clear. Therefore, this paper discusses the YAP/TAZ-binding proteins, involved pathways, and related pathological processes in the development of inflammatory bowel disease and intestinal cancer disease.

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Abstract

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Keywords: YAP/TAZ, TEAD, Smad2/3, Hippo, Notch, Wnt, inflammatory bowel disease, intestinal cancer

Running title: Overview of YAP/TAZ in intestinal diseases

Introduction

YAP (Yes-associated protein) and TAZ (transcriptional coactivator with WW and PDZ domains; WWTR1) were initially considered novel transcriptional coactivators interacting with the TEAD family of DNA-binding

transcription factors [1]. YAP/TAZ are replication inhibitors that promote cell proliferation, stem cell maintenance and tissue stability[2]. YAP/TAZ acts as a sensor for the structural and mechanical characteristics of the cellular microenvironment [3,4]. They shuttle between the cytoplasm and nucleus in response to multiple inputs[5]. The subcellular localization of YAP is regulated by Ser phosphorylation (127) [6], while the localization of YAP/TAZ is further affected by cytoskeletal components involved in morphological changes, receptor-mediated signaling, as well as cytoplasmic and nuclear actin[7-9]. Nuclear YAP/TAZ promotes cell proliferation, organ overgrowth, stress survival, and postmitotic cell dedifferentiation into their respective tissue progenitors[10]. Activation of YAP/TAZ reflects the 'social' behavior of cells, including cell adhesion and mechanical signals obtained by the structure of the cell organization and extracellular pericellular tissues[4]. It is proven that simultaneous revitalization discourse or excessive YAP/TAZ leads to the transformation and development of the above tumor cells[11]. In contrast, MEK/MAPK inhibitors[12,13] and γ-secretase inhibitors (GSIs)[14] have the ability to actively reduce YAP/TAZ levels. YAP/TAZ is not required for the normal physiology of most adult organs but plays an important role in organ growth during embryonic development and in promoting tissue repair after adult tissue injury. Intestinal diseases are mainly inflammatory and based on tumors. YAP/TAZ plays an important role in this process. Therefore, this article discusses the YAP/TAZ protein connection involving the relevant sick leave business processes and with intestinal diseases the most indicated intestinal disease processes.

Binding of transcription factors

Binding to TEAD

YAP and TAZ do not have DNA binding domains, and they need to bind transcription factors to enter DNA. YAP/TAZ mainly utilizes the TEAD family of transcription factors to induce most of its biologically relevant gene expression programs [15,16]. Under favorable conditions, YAP and TAZ actively promote cell growth through a transcriptional program mediated by TEAD family transcription factors[10]. Through these factors, YAP/TAZ binds to DNA and co-occupies chromatin with activin-1 (AP-1, JUN and FOS protein dimers) at complex cis-regulatory elements containing TEAD and AP-1 motifs. YAP/TAZ/TEAD and AP-1 form a complex that synergistically activates target genes directly involved in the control of S-phase entry and mitosis. The AP-1 transcription factor, one of the most well-characterized immediate early gene products, is formed by dimerization of Fos family proteins (Fos, FOSB, FRA1 and FRA2) and Jun family proteins (Jun, JUNB and JUND) [17]. As a heterodimer, AP-1 binds to the promoter regions of specific target genes and translates extracellular signals into changes in gene expression[18]. Upon activation, YAP/TAZ translocates into the nucleus and binds to TEAD transcription factors, interacts with chromatin remodeling factors, and regulates RNA polymerase II (Pol II) to drive or repress the expression of target genes and promote the transcriptional program. Proliferation or cell specificity mainly includes the cell cycle, cell migration and cell fate regulators[18,19]. Interestingly, the YAP/TAZ-TEAD complex can be disrupted by two very different mechanisms, one of which is the direct inhibition of TEAD-binding protein fragments: Ω-loop or α-helix[11], and the other is the formation of complexes with YAP/TAZ by other substances to replace the association between YAP/TAZ and the DNA binding platform TEAD. A study found that ARID1A-SWI/SNF complexes precisely inhibit the transcriptional coactivator YAP/TAZ through ARID1A-mediated YAP/TAZ and SWI/SNF complexes [20,21].

Binding to Smad2/3

In embryonic stem cells, YAP/TAZ was shown to interact directly with Smad2/3, and its interaction may occur in the cytoplasmic and nuclear compartments while regulating nuclear accumulation[22]. After YAP/TAZ downregulation, the interaction of Smads2/3 with YAP/TAZ was evident in tubular epithelial cells, reducing the accumulation of nuclear Smad2 and Smad3[22]. During fibrosis, Smad transcription factors are canonical mediators of profibrotic TGF-β responses[23]. An important step in TGF-β-induced fibroblast activation is the C-terminal phosphorylation of the profibrotic transcription factors Smad2 and Smad3. Phosphorylated Smad2/3 accumulates in the nucleus, where it drives the expression of TGF-β-sensitive profibrotic genes [24]. In turn, TGF-β induces YAP/TAZ to bind to the Smad2/3-4 complex and is recruited to the TGF-β response element to regulate the expression of target genes, while the loss of YAP/TAZ leads to the inhibition

of TGF-β signaling[25,26].

Table 1 YAP/TAZ-bound transcription factors

Binding transcription factor	dependent interaction
RUNX	RUNX2 cooperates with YAP/TAZ to promote the transformation of epithelial cells into
KLF4	The coexpression of YAP/TAZ and KLF4 promote differentiation, while knockdown of K
TBX5	YAP/TAZ can stimulate TBX5 transcription by interacting with multiple domains.
NKX2-1	YAP/TAZ and extended TEAD direct NKX2-1 to its AT1-specific site and prevent it fro
Bmp4	Bmp4 is a target of endothelial YAP/TAZ during osteogenesis . Cyclic activation of YAP
Ncoa6	The Ncoa6 subunit has been shown to interact with mammalian YAP/TAZ to methylate

Signaling pathways involved in YAP/TAZ

Hippo signaling pathway

The Hippo pathway regulates tissue growth and cell fate and is considered a central regulator of tissue homeostasis and organ size[40-43]. The Hippo pathway can receive upstream stimuli, such as hypoxia, and can also interact with other pathways to convert signals into intracellular responses[37]. YAP/TAZ is a multifunctional transcriptional activator that is a downstream effector of the Hippo pathway, plays a negative regulatory role, participates in a variety of cellular responses and is closely related to cell proliferation and metabolism [44]. Under the regulation of the Hippo pathway, YAP/TAZ can enter the nucleus, combine with TEAD transcription factors to form a complex, and be recruited to specific target promoter sequences, thereby regulating gene expression during cell growth and other developmental processes and promoting tissue remodeling [43,45-47]. At the heart of the Hippo pathway is a kinase cascade in which Mst1/2 kinases and SAV1 form a complex that phosphorylates and activates LATS1/2[48]. LATS1/2 kinases in turn phosphorylate and inhibit the transcriptional coactivator YAP/TAZ[49]. YAP/TAZ phosphorylation prevents its nuclear localization and leads to cytoplasmic sequestration by binding to the 14-3-3 adaptor protein. Furthermore, YAP/TAZ can be targeted for degradation through subsequent phosphorylation of casein kinase 1[39,45]. Inactivation or loss of MST1/2 and LATS1/2 can lead to dephosphorylation and nuclear translocation of YAP/TAZ [31]. After dephosphorylation, YAP/TAZ is transported to the nucleus and interacts with other transcription factors to induce gene expression that promotes cell proliferation and inhibits apoptosis [31]. As one of the main effector proteins downstream of the Hippo pathway, YAP/TAZ is regulated by cell and tissue structure and is also affected by other signals, including mechanotransformation, Wnt signaling, and Notch metabolic signaling [50].

Notch signaling pathway

Notch signaling is frequently involved in development and homeostasis in multiple tissues, resulting in diverse cellular responses, and Notch activity regulates growth, differentiation, survival, and stem cell behavior in a highly context-dependent manner[51,52]. Notch controls binary cell fate during morphogenesis, whereas YAP/TAZ translates the physical properties of the microenvironment into key cellular decisions [53]. Notch and YAP-TEAD drive the specification of trophectoderm fate downstream of cell polarity by activating the expression of the trophectoderm-specific gene Cdx2 in combination with trophectoderm-specific enhancers [54]. YAP/TAZ can act upstream of Notch signaling by activating Notch receptors[53]. For example, during postinflammatory intestinal repair, the Notch signaling pathway is downstream of YAP/TAZ activation [3]. YAP/TAZ is activated in tip cells through actomyosin tension-mediated GPCR signaling, LPA4 and LPA6 during angiogenesis. YAP/TAZ controls neovascularization by blocking β-catenin-NICD-mediated expression of the Notch ligand Dll4 [55]. In the corneal epithelium, Notch deletion triggers inflammatory cytokine secretion and continues the cycle of injury and repair [56,57]. This persistent inflammation causes ECM deposition and fibrosis, leading to activation of YAP/TAZ mechanotransduction [58]. Both in vitro and in vivo experiments have shown that low cell density or high ECM rigidity can trigger the activation of YAP/TAZ-TEAD in basal progenitor cells to maintain them via inhibiting Notch signaling[59]. In basal

progenitors, the YAP/TAZ-TEAD complex activates the transcription of Dll1 and Dll3; then, cis-interaction of Dll1 and Dll3 with Notch receptors can block Notch activation, thereby preventing epidermal differentiation [59].

Wnt signaling pathway

Wnt growth factors play prominent pleiotropic roles in cell–cell communication, including the control of cell fate, proliferation, and stem cell maintenance [60]. Studies have found that YAP/TAZ is a downstream effector of the Wnt signaling pathway[4,61]. YAP/TAZ is a component of the β-catenin destruction complex. In the absence of Wnt ligands, YAP/TAZ binds to Axin and recruits β-TrCP to degrade β-catenin. In the presence of Wnt ligands, YAP/TAZ is released from the complex, and β-catenin enters the nucleus, thus activating the pathway [60]. Wnt5a/b and Wnt3a induce YAP/TAZ activation to promote YAP/TAZ activation and TEAD-mediated transcription [61]. The study also found that the Wnt3a/EGF signaling pathway induces the nuclear translocation of YAP/TAZ by expressing Arl4c in the predilated duct, and YAP/TAZ enhances the expression of Arl4c induced by Wnt3a/EGF[62]. The Wnt signaling pathway can transcriptionally induce the expression of YAP/TAZ and TEAD1/2/4. YAP/TAZ is normally only localized to the nucleus in crypt basal stem cells, but during intestinal regeneration or organoid growth, YAP/TAZ is present in the nucleus in most intestinal epithelial cells in a Src family kinase-dependent manner. Thus, Wnt and SrcYAP/TAZ signaling together promote intestinal regeneration [63]. However, YAP/TAZ and TEAD jointly block the induction of mesoderm genes by SMAD2/3, indicating that the Wnt/β-catenin and SMAD2/3 pathways jointly inhibit YAP/TAZ and promote the EMT process[64].

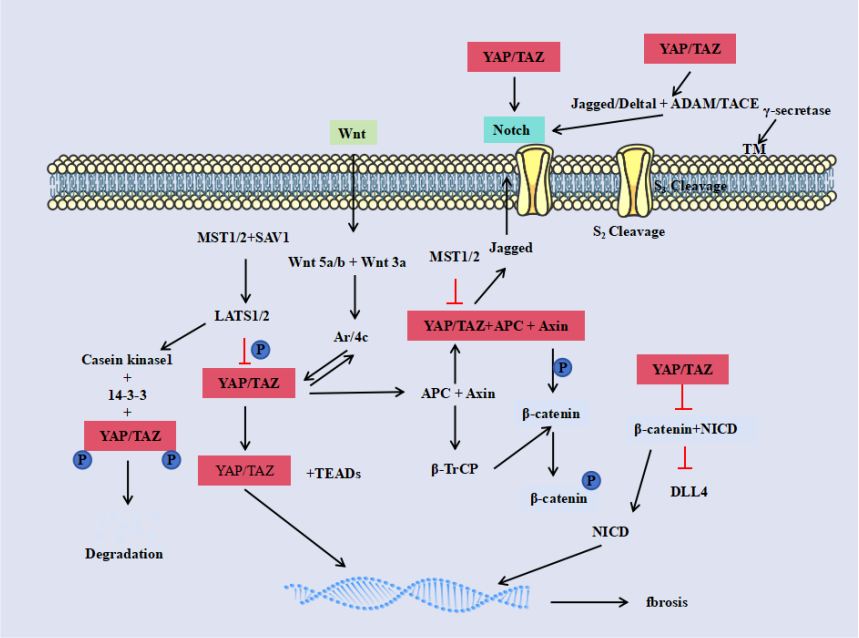

Figure1 Signaling pathways involved in YAP/TAZ

Figure1:Mst1/2 kinases and SAV1 form a complex that phosphorylates and activates LATS1/2 [48]. LATS1/2 kinases in turn phosphorylate and inhibit the transcriptional coactivator YAP/TAZ. YAP/TAZ phosphorylation prevents its nuclear localization and leads to cytoplasmic sequestration by binding to the 14-3-3 adaptor protein. Furthermore, YAP/TAZ can be targeted for degradation through subsequent phosphorylation of casein kinase 1. Inactivation or loss of MST1/2 and LATS1/2 can lead to dephosphorylation and nuclear translocation of YAP/TAZ. YAP/TAZ block β-catenin-NICD-mediated expression of the Notch ligand Dll4.

In the presence of Wnt ligands, YAP/TAZ is released from the complex, and β-catenin enters the nucleus, thus activating the pathway .

Table 2 Other pathways involved in YAP/TAZ

Participate in the pathway	References
Rho-ROCK1 signaling pathway	As a nuclear transmission mechanical signal, YAP/TAZ activity is triggered by ECM stiff
TGF-β signaling pathway	In human dermal fibroblasts, YAP/TAZ cooperates with the transcription factors AP-1 a
PI3K signaling pathway	The Hippo tumor suppressor pathway restricts growth factor receptor signaling through t
GPCR signaling pathway	Conjugation of GPCRs to Gα12/13, Gαq/11 or Gαi/o (e.g., LPA, thrombin receptors) act
KRAS signaling pathway	KRAS induces posttranscriptional modification of YAP/TAZ and enhances its transcripti
EGFR signaling pathway	YAP/TAZ silencing reduces maintenance of resistance, whereas YAP/TAZ overexpression

Involved related pathological processes

Relationship between YAP/TAZ and inflammation

An appropriate inflammatory response is critical for the restoration of tissue homeostasis after injury or infection, but how this response is regulated by the physical properties of the cellular and tissue microenvironment is not fully understood [47]. Recently, multiple studies have revealed the role of YAP/TAZ in regulating inflammatory and immune responses [74]. YAP/TAZ are primary sensors of the cellular microenvironment, integrating cell polarity and mechanical signaling with growth factor signaling and inflammation [4]. YAP/TAZ-dependent function is associated with the termination of NF-κB-dependent transcription of inflammatory genes by inducing IκBa expression[75]. Deletion of YAP/TAZ increases the expression of inflammatory genes, resulting in elevated local inflammation and enhanced accumulation and persistence of inflammatory cells[76]. Activation of the downstream molecules of the Hippo pathway YAP/TAZ in hepatocytes can promote the expression of inflammatory (TNF, IL1β) proteins, thereby stimulating hepatic inflammation [77]. Additionally, increased nuclear expression of YAP/TAZ, a mediator of the Hippo pathway in lung epithelial type II cells, promotes AECII activity, whereas mice lacking YAP/TAZ exhibit prolonged pulmonary inflammatory responses during bacterial pneumonia and alveolar epithelial regeneration delay[76]. In the corneal epithelium, persistent inflammation causes ECM deposition and fibrosis, leading to activation of YAP/TAZ mechanotransduction [58]. In this process, NF-κB is considered to be one of the important targets of YAP/TAZ and plays an anti-inflammatory role in regulating innate immunity and autoimmunity [76,78,79]. Phosphorylated YAP is sufficient to reduce inflammation in osteoarthritis by inhibiting the NF-κB signaling pathway[78]. Overexpression of constitutively active TAZ significantly reduces the secretion of inflammatory cytokines caused by overactivation of the NF-κB pathway and Rictor siRNA transfection. The Rictor/mTORC2 signaling pathway inhibits inflammation by inhibiting YAP/TAZ degradation and YAP/TAZ nuclear translocation[74].

Relationship between YAP/TAZ and fibrosis

Recent studies have demonstrated aberrant activation of YAP/TAZ in fibrosis in both animal models and human tissues[66]. YAP/TAZ is activated in response to increased mechanical stress, such as when cells adopt a diffuse cell morphology, undergo adhesion to a hard ECM, or deform due to substrate topology. All of these conditions affect the structural organization of the F-actin cytoskeleton, thereby favoring localized adhesion and actin stress fiber formation [58]. In fibroblasts, ECM stiffness mechanically activates YAP/TAZ, promoting the production of profibrotic mediators and ECM proteins. This results in tissue stiffness, which establishes a feedforward loop of fibroblast activation and tissue fibrosis. In contrast, in epithelial cells, YAP/TAZ is activated by disruption of cell polarity and increased ECM stiffness in fibrotic tissue, thereby promoting epithelial cell proliferation and survival [80].

YAP/TAZ and tissue, organ regeneration and wound healing

YAP/TAZ has recently been shown to be a key mediator of wound healing and tissue regeneration in response

to tissue damage[1]. During these processes, YAP/TAZ is activated by intracellular and external signals [2]. During skin wound healing, YAP/TAZ-mediated nuclear signaling is indispensable for TGF-β signaling [81]. Mechanistically, calcitriol promotes crosstalk between the YAP/TAZ and TGF-β/Smad signaling pathways, triggering EMT in keratinocytes during wound healing[82]. Extensive work has identified YAP/TAZ as key regulators of cell proliferation and 'stemness', especially during organ growth and regeneration [83]. Exciting results have been observed in mice stimulating organ repair and regeneration in nonregenerative organs [84]. The mouse heart is currently the most prominent example of the beneficial regenerative effects of experimental activation of YAP/TAZ, but activation of YAP/TAZ also contributes to the regeneration of other organs in adult mice, including the liver [85], muscle, and gut[84,86]. These studies raise the possibility of manipulating YAP/TAZ downstream of the Hippo pathway in injured human organs as a means to stimulate regeneration of endogenous mechanisms. However, therapeutic activation of YAP/TAZ for regeneration may have significant risks, as its overactivation has been shown to promote cancer development [84].

Role in gut-related diseases

The role of YAP/TAZ in inflammatory bowel disease

Crohn's disease is a major form of inflammatory bowel disease characterized by chronic inflammation, recurrent mucosal healing and deposition of extracellular matrix (ECM) in the mucosa and submucosa, leading to the development of structural fibrosis and intestinal obstruction[87]. YAP/TAZ expression is significantly upregulated in stenotic fibroblasts, which correlates with the YAP/TAZ target gene signature. Downregulation of YAP/TAZ genes inhibits intestinal fibroblast activation. In intestinal fibroblasts, YAP/TAZ is activated by the Rho-ROCK1 signaling pathway. The high expression of YAP/TAZ is positively correlated with the expression of ROCK1, which is a prognostic marker of intestinal obstruction in CD patients [66]. Meanwhile, the YAP/TAZ and TEAD1/2/4 genes are also transcriptionally regulated by the Wnt/β-catenin signaling pathway in the intestine, and the nuclear translocation of YAP/TAZ in tissue injury depends on the Src family kinase signaling pathway. Therefore, when Src family kinases inhibit LATS1/2, thereby driving YAP/TAZ to the nucleus, they activate YAP/TAZ-TEAD-mediated transcription, thereby promoting intestinal tissue regeneration [63]. The study also found that the IL-6 coreceptor gp130 is activated during intestinal inflammation, and the expression of a constitutively active form of gp130 is activated and requires YAP/TAZ to induce enterocyte proliferative responses and intestinal regeneration in a model of inflammatory colitis. Targeted inhibition of YAP/TAZ in fibroblasts may be a potential therapeutic strategy to inhibit intestinal fibrosis in CD[66].

The role of YAP/TAZ in intestinal cancer

YAP/TAZ are potent inducers of cell proliferation and, in many cases, important drivers of tumorigenesis [4,19,88]. Activation or overexpression of YAP/TAZ has been shown to lead to cellular transformation, tumor growth, metastasis and drug resistance[1,11]. Colorectal carcinogenesis typically begins with constitutive WNT signaling, resulting in nuclear accumulation of transcriptional coactivators, including YAP/TAZ. Thereafter, mutations and epigenetic events follow, inducing genetic programs that drive invasion and metastasis [89]. Consistently, TIAM1 was found to be part of a cytoplasmic destruction complex that regulates TAZ/YAP stability. It was further found that, in naive intestinal epithelial cells, when the destruction complex is inactivated, TIAM1 and TAZ/YAP aggregate and translocate from the cytoplasm to the nucleus. However, in the nucleus, TIAM1 continues to antagonize nuclear TAZ/YAP function despite the formation of WNT signaling, thereby inhibiting cell migration and invasion. In the cytoplasm, TIAM1 localizes to the destruction complex and promotes TAZ degradation by enhancing its interaction with bTrCP. Nuclear TIAM1 inhibits the interaction of TAZ/YAP with TEADs and suppresses the expression of TAZ/YAP target genes involved in epithelial-mesenchymal transition, cell migration and invasion, thereby inhibiting the migration and invasion of colorectal cancer cells [89]. The Hippo pathway in mammals can also inhibit the phosphorylation of YAP/TAZ by the large tumor suppressor (LATS) family of Hippo core kinases via interaction with 14-3-3 proteins and/or via the ubiquitin–proteasome pathway. Degradation leads to cytoplasmic septum to inhibit intestinal tumor development [15,90,91]. YAP and TAZ are downstream molecules of the Hippo pathway and are widely expressed in human tissues under normal physiological conditions. When the

Hippo kinase module is repressed, YAP and TAZ lose their phosphorylation and translocate to the nucleus, inhibiting apoptosis and promoting EMT and tumor formation. YAP can also suppress the activity of the Hippo pathway by activating the PI3K/AKT pathway. The PI3K/AKT pathway is a critical transduction pathway involved in regulating cell proliferation, and enhancement of PI3K activity contributes to AKT activation and promotes the continued growth of tumor cells[92]. On the other hand, the transcriptional coactivators YAP/ TAZ act as key regulators of the conserved CRC gained enhancers. The same YAP/TAZ-bound enhancers display active chromatin profiles across diverse human tumors, highlighting a pan-cancer epigenetic rewiring which at single-cell level distinguishes malignant from normal cell populations. YAP/TAZ inhibition in established tumor organoids causes extensive cell death unveiling their essential role in tumor maintenance. The epigenetic landscape of human CRC unveils the existence of an aberrant pan-cancer core of enhancers regulated by the transcriptional coactivators YAP/TAZ and active in more than 20 types of human malignancies[93].

Conclusion and prospects

YAP/TAZ acts as a homologous transcriptional coactivator and plays an important role in promoting cell proliferation, stem cell maintenance, and tissue homeostasis. In the inflammatory process, the deletion of YAP/TAZ can increase the expression of inflammatory genes, leading to an increase in local inflammation, the accumulation of inflammatory cells and an increase in persistence. Simultaneous activation or overexpression of YAP/TAZ has been shown to lead to cellular transformation and tumor development. The persistent inflammatory response, in turn, leads to abnormal activation of YAP/TAZ and promotes local adhesion and the formation of actin stress fibers, which subsequently leads to fibrosis. Overactivated YAP/TAZ can lead to cell proliferation, metastasis, and EMT. Therefore, YAP/TAZ play an important role in the process of intestinal disease. YAP/TAZ can regulate the development of inflammation and the formation of fibrosis in the later stages of intestinal inflammatory diseases. YAP/TAZ, which is overactivated in intestinal tumor diseases, promotes cell transformation, tumor growth, metastasis, and drug resistance. YAP/TAZ is a multifunctional transcriptional activator that is a downstream effector of the Hippo and Wnt pathways, plays a negative regulatory role, participates in a variety of cellular responses and is closely related to cell proliferation and metabolism. In addition, YAP/TAZ can act upstream of Notch signaling by activating Notch receptors. Therefore, this paper discusses the proteins related to YAP/TAZ binding, the related pathways involved, the related pathological processes, and their role in intestinal diseases. However, other relevant binding proteins and mechanisms of action of YAP/TAZ in the course of intestinal disease have yet to be discovered. We suspect that regulating the expression of YAP/TAZ by regulating YAP/TAZ-related proteins and pathways can improve the occurrence and development of intestinal diseases. As people pay increasing attention to the role of YAP/TAZ in disease, more regulatory mechanisms will be mined and make a major achievement. Next step, we will study the clinical application of YAP/TAZ in intestinal diseases and make the discovery of these mechanisms benefit patients.

Author Contributions

LQH designed the work. RJ and YQC contributed equally to this work, wrote the manuscript and prepared the figures. ZXJ and GHL drafted and revised the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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