SPANDIDOS PUBLICATIONS

MOLECULAR MEDICINE REPORTS 22: 4101-4106, 2020

YAP-mediated crosstalk between the Wnt and Hippo signaling pathways (Review)

LIYA JIANG[1,2], JUAN LI[1,2], CHENXING ZHANG[1], YUFENG SHANG[1,2] and JUN LIN[1,2]

[1]Department of Stomatology, The First Affiliated Hospital, College of Medicine, Zhejiang University; [2]Key Laboratory of Oral Biomedical Research of Zhejiang Province, Zhejiang University School of Stomatology, Hangzhou, Zhejiang 310006, P.R. China

Received February 6, 2020; Accepted August 18, 2020

DOI: 10.3892/mmr.2020.11529

Abstract. Yes-associated protein (YAP) acts as a transcriptional co-activator in gene expression and cell proliferation control by binding to the transcriptional factor TEA domain (TEAD) of the Hippo signaling pathway in the nucleus, and also acts as a regulator by binding to another transcriptional co-activator, β-catenin of the Wnt signaling pathway. Whether YAP preferentially acts as a transcriptional co-regulator of the activity of the Hippo signaling pathway or as a regulator in the Wnt signaling pathway depends on the cell type. Nuclear YAP upregulates the expression of β-catenin, while cytoplasmic YAP has a negative effect on this expression. The present mini-review focused on the important roles of YAP and further discussed the cross-links between the Wnt and Hippo signaling pathways. The Wnt and Hippo signaling pathways are both related to the development of fibrosis or cancer. The current review discussed treatment approaches for these conditions based on the two pathways. YAP, the intersection of these two signaling pathways, has the potential to be developed as a novel treatment target, according to previous basic studies on fibroblasts and cancer cells.

Contents

1. Introduction
2. YAP complex in the Hippo and Wnt signaling pathway
3. YAP serves a key role in controlling organ size
4. YAP is a transcriptional co-activator or a regulator depending on the cell type
5. YAP has both negative and positive influences on the Wnt signaling pathway
6. Inspiration of new routes for future treatment
7. Conclusion

Correspondence to: Professor Jun Lin, Department of Stomatology, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qinchun Road, Hangzhou, Zhejiang 310006, P.R. China
E-mail: junlin2@zju.edu.cn

Key words: cancer, β-catenin, fibrosis, TEA domain, Wnt, Yes-associated protein

1. Introduction

Yes-associated protein (YAP) is a transcriptional co-activator in the Hippo signaling pathway, a pathway that is universally regarded as a key regulator of organ size and tissue homeostasis by controlling cell proliferation and apoptosis. A recent study revealed that Hippo is even able to reprogram different cell types into their corresponding tissue-specific stem cells (1). In the upstream part of the Hippo signaling pathway, Ste20 family kinases [macrophage stimulating 1 (Mst1) and Mst2] are activated and cause a kinase cascade reaction. Furthermore, these two proteins phosphorylate tumor suppressor homolog large tumor suppressor kinases (Lats), and Lats kinases then phosphorylate YAP (2-5). Phosphorylated YAP associates with 14-3-3 protein and remains in the cytoplasm while unphosphorylated YAP controls the gene expression by binding to transcriptional factor TEA domain (TEAD) in the nucleus (6-8). The Hippo signaling pathway may be affected by various factors, including mechanical stress, cell polarity, extracellular stimulus and interaction of upstream regulating factors. Furthermore, the promotion of osteogenic differentiation activity was observed in response to mechanical stimuli using magnetically responsive coatings, as reported in previous studies by our group (9,10); the literature search and analysis for the present review aimed to identify whether Hippo is the major signaling pathway in controlling this process.

YAP is also a regulator in the Wnt signaling pathway by binding to β-catenin, another transcriptional co-activator in Wnt. This pathway serves an important role in homeostatic mechanisms, and β-catenin expression regulates various biological processes, such as cell proliferation, differentiation, adipogenesis and aging (11,12). A recent study revealed that in neural stem cells, the binding of β-catenin-YAP has a stronger function compared with YAP-TEAD (13). Furthermore, elucidation of the linking role of YAP of the Hippo and Wnt signaling pathways may facilitate the understanding of the regulation and homeostasis and may have a clinical significance for future treatment strategies.

2. YAP complex in Hippo and Wnt signaling pathways

Since YAP does not have any DNA-binding domains, it acts via target transcriptional factors to stimulate gene expression. TEAD is one of these transcriptional factors and chromatin immunoprecipitation-on-chip experiments indicated that TEAD occupies a more similar set of gene promoters to YAP compared with other transcriptional factors (6,14). The same results have also been demonstrated via gene set enrichment analysis, suggesting that this is not a random event.

In the Wnt signaling pathway, YAP is a downstream effector of the non-canonical Wnt axis. Previously, it was indicated that YAP and β-catenin are recruited to genes via the TEAD and T cell factor (TCF)/lymphoid enhancer factor-1 family of transcriptional factors, respectively (7). The present understanding is that YAP is involved in regulating tissue differentiation and migration of tumor cells by binding to β-catenin (15). In cells where the Wnt signaling pathway is inactivated, YAP binds to the destruction complex together with β-catenin in the cytoplasm, which is not only useful for β-catenin's localization in the cytoplasm but also essential in β-catenin inactivation (Fig. 1A). This process does not have any effect on the stability of β-catenin but suppresses its transcriptional activity (15). In cells where the Wnt signaling pathway is activated, YAP is released from the destruction complex, and without guidance from the destruction complex, YAP migrates from the cytoplasm to the nucleus and serves its role to activate the Hippo pathway (Fig. 1B) (16,17).

3. YAP serves a key role in controlling organ size

YAP induces cell proliferation, which is of great significance for tissue growth and organ development. In humans, connective tissue growth factor (CTGF) is a YAP-regulated target gene and the interaction between YAP and TEAD is a necessity to induce it. It is reported that blocking CTGF by mutating TEAD causes Sveinsson's chorioretinal atrophy (6). In *Drosophila*, large eyes were observed in subjects that overexpressed both the YAP homolog Yorkie and the TEAD homolog Scalloped, and animals only expressing Yorkie have small eyes (6). Another experiment in *Drosophila* demonstrated that YAP is involved in organ size control via the Wnt signaling pathway, and mutation of YAP leads to excessive proliferation of imaginal discs (8). Furthermore, Wnt controls cell proliferation and apoptosis, and is involved in tissue and organ development. Silencing of YAP attenuates the effect of β-catenin, suggesting that YAP effectively modulates the transcriptional activation of Wnt/β-catenin signaling molecules (18). In mice, nuclear β-catenin accumulation causes cystic kidneys (19), and transgenic mice that expressed an activated mutant of β-catenin developed cysts (20). Therefore, it was indicated that YAP may be essential for the normal functioning of Wnt/β-catenin.

4. YAP is a transcriptional co-activator or a regulator depending on the cell type

Only a small number of previous studies have investigated whether YAP-TEAD or YAP-β catenin has the more significant function, as they are influenced and modulated by each other. That is to say, the role of YAP in the body, as a transcriptional co-regulator or a regulator, requires further studies. It has been indicated that the cell type is the major factor determining the role of YAP. For instance, in neural stem cells, the binding activity of YAP-β-catenin was reported to have a stronger function on neuronal differentiation compared with TEAD (13), which is different from previous results obtained with mesenchymal stem cells (21). Furthermore, these results are surprising because YAP is a well-known transcriptional co-activator that binds to TEAD in the Hippo pathway, but it acts as a regulator of the Wnt signaling pathway. Whether the cell is healthy is also an influencing factor. It was revealed that YAP knockout is able to overcome the rapid demise of mice with adenomatous polyposis coli (APC) deficiency, and it was suggested that both the Wnt and the Hippo pathway may be involved in this process (16). In healthy cells, β-catenin/Wnt controls homeostasis and YAP acts as a regulator. In cells exposed to different conditions, such as APC deficiency, tumorigenesis or regeneration, YAP prefers the transcriptional co-regulatory activity in the Hippo pathway. Therefore, whether YAP acts as a transcriptional co-activator in the Hippo pathway or a regulator in the Wnt pathway depends on the cell type. While the underlying mechanisms remain elusive, it was proved that rigid matrix stiffness promotes the nuclear localization and activity of YAP (22). It was speculated that different cell types may activate different mechanisms according to matrix stiffness, thereby determining the role of YAP. Therefore, further studies are required to elucidate the underlying mechanisms.

While YAP-TEAD and YAP-β-catenin are discussed separately, they may occasionally bind to each other. YAP is the target of Wnt/β-catenin, and it is able to directly bind to the N-terminal domain of β-catenin. The TCF-β-catenin-YAP-TEAD complex then transfers into the nuclear and locates to the common gene of TEAD and TCF (Fig. 2). A previous study revealed that the β-catenin-induced localization to the Oct4 distal enhancer is TEAD-dependent and also demonstrated the occurrence of the YAP-TEAD-β-catenin trimeric complex (23). Thus, the crosstalk between Hippo and Wnt is complex.

5. YAP has both negative and positive influences on the Wnt signaling pathway

It has been reported that cytoplasmic YAP has a negative regulatory effect on the Wnt signaling pathway (24). YAP is phosphorylated by upstream factors in the Hippo pathway. When Wnt is activated, phosphorylated YAP and β-catenin are dislodged from the complex and two routes are involved in the regulation of the Wnt signaling pathway. One of these routes is that the phosphorylated YAP may impede nuclear β-catenin localization by combining and sequestering Dishevelled 2 in the cytoplasm (8,25). Alternatively, Src homology 2 domain tyrosine phosphatase (SHP2), an amino acid phosphatase, promotes the transcription of β-catenin after it translocates into the nucleus. Thus, once YAP locates SHP2 in the cytoplasm, Wnt signaling pathway activation is dampened (Fig. 1B) (26-28).

A previous study revealed that in osteoblast-lineage cells, reduced β-catenin protein expression was present in YAP-deficiency cells in culture and *in vivo*, and the expression

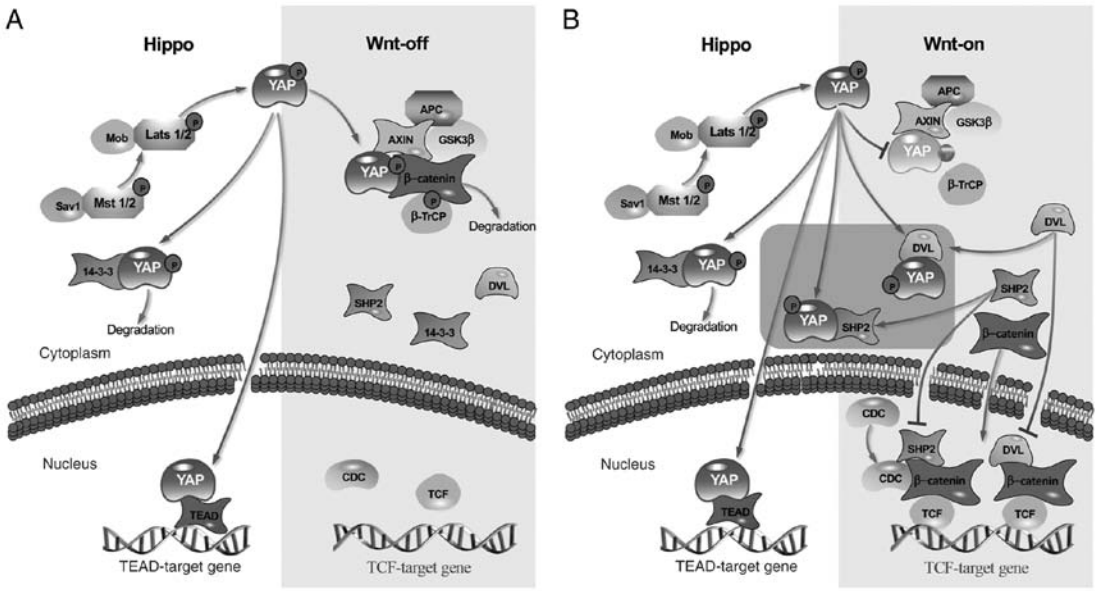

Figure 1. Cytoplasmic YAP has a negative regulatory effect on the Wnt signaling pathway. In the Hippo pathway, phosphorylated YAP binds to 14-3-3 protein and remains in the cytoplasm, while unphosphorylated YAP migrates into the nucleus to bind to TEAD. (A) When Wnt signaling is inactive, the phosphorylated YAP and β-catenin are located in the cytoplasm by joining the destruction complex together with various other factors. (B) When Wnt signaling is active, YAP and β-catenin dissociate from the complex. The phosphorylated YAP binds to Dvl and SHP2 in the cytoplasm and stops them from migrating into the nucleus and activating β-catenin-TCF binding. Mechanisms are highlighted with grey squares. TEAD, TEA domain; YAP, Yes-associated protein; Dvl, Dishevelled; SHP2, Src homology 2 domain tyrosine phosphatases; TCF, T cell factor; Sav, salvador; Lats1/2, warts-*Drosophila*; Msts1/2, Hippo-*Drosophila*; APC, adenomatous polyposis coli; GSK-3β, glycogen synthase kinase-3β; β-TrCP, β-transducin repeats-containing proteins; CDC, cell division cycle gene.

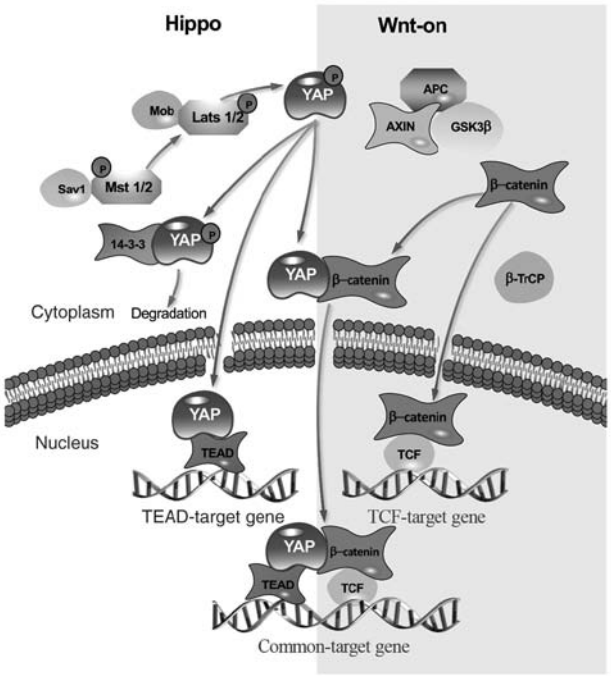

Figure 2. YAP-TEAD-β-catenin-TCF complex. When Wnt signaling is active, YAP binds to the N-terminal domain of β-catenin and moves into the nucleus together. As YAP and β-catenin interact with TEAD and TCF separately, the complex locates to the common target gene of TEAD and TCF. TEAD, TEA domain; YAP, Yes-associated protein; TCF, T cell factor; Sav, salvador; Lats1/2, Warts-*Drosophila*; Msts1/2, Hippo-*Drosophila*; APC, adenomatous polyposis coli; GSK-3β, glycogen synthase kinase-3β; β-TrCP, β-transducin repeats-containing proteins.

of YAP increases the expression of β-catenin (29). Thus, YAP has a positive effect on the Wnt signaling pathway. Similar results were reported in other studies. For instance, using an *in vitro* model of mouse chondrogenic cells, YAP was demonstrated to upregulate β-catenin to control chondrocyte differentiation (30). In an *in vivo* study, YAP was indicated to act via a β-catenin-dependent mechanism in muscle cells to control neuromuscular junction formation and regeneration (31). The observed positive regulation was different from those of previous studies, as the experimental subject was nuclear YAP. As mentioned above, the roles of YAP may differ depending on the cell type, and there may be cell type-dependent differences in terms of whether the nucleus or cytoplasm is the site for YAP to regulate β-catenin. It was speculated that in the nucleus, YAP and β-catenin act together, while they are negatively associated in the cytoplasm, which is based on the result that YAP in the nucleus promotes SHP2 translocation into the nucleus, which activates the transcription of β-catenin (27). However, as the positive regulatory interaction between the two signaling pathways has only been discovered in recent years, future investigations are required.

6. Inspiration of new routes for future treatment

Treatment of fibrosis. Fibrosis is a pathological process that results from the deposition and insufficient resorption of extracellular matrix (ECM). The Wnt signaling pathway serves a pivotal role in fibroblast activation and the epithelial-to-mesenchymal transition process (32), contributing to the dynamic deposition of ECM and an increase of ECM stiffness. Thus, Wnt has been proposed as a target of fibrosis treatment. ICG-001 (33), Klotho (34) and poricoic acid (35) have all been indicated to attenuate Wnt and reverse fibrosis. In recent years, the Hippo pathway has been suggested to be involved in the development of fibrosis (36). YAP may be considered as a

novel target for the treatment of fibrosis, as the diminishment of nuclear YAP localization is associated with inhibition of the Wnt signaling pathway. Previous studies aimed to control nuclear YAP localization to treat fibrosis (37,38). Furthermore, it was demonstrated that highly specific inhibitors may be developed based on the protein-protein interactions located at the intersection of the Hippo and Wnt signaling pathways, which may be used as a novel target (39).

Treatment for cancer. In cancer stroma, fibrotic processes occur to various degrees, which may lead to fibrosis, and there is a close association between fibrosis and cancer. The Wnt and Hippo signaling pathways modulate the features of cancer cells (40-42), and identifying targets on these two signaling pathways has been a hot research topic. Certain previous studies have also focused on both pathways simultaneously (43-45).

The Wnt signaling pathway has been indicated to be involved in cancer regulation via persistent activation of β-catenin signaling (12,46). The involvement of the YAP-β-catenin complex is important. For instance, in colon cancer, the β-catenin-YAP1-T-box transcription factor 5 complex was identified to promote the survival and transformation of β-catenin-active cancer cell lines. By examining the top 50 genes in proliferating β-catenin-active cells, a significant enrichment of proteins associated with YAP was identified (47). In hepatoblastoma cells, only the combination of β-catenin and YAP caused rapid cell proliferation and then induced cancer, but this effect was not observed with β-catenin or YAP alone (46). Based on these results, Ras association domain family 1A gene was used to inhibit the binding of YAP (23), and ICG-001, a small molecule inhibitor, was used as a target for head and neck cancer by regulating β-catenin/Wnt (48).

YAP binds to TEAD to induce proliferation while entering the nucleus, and is degraded when binding to 14-3-3 protein in the cytoplasm (25); this is also the mechanism in the Hippo signaling pathway resulting in dysregulated cell proliferation. In previous studies, different medicines, such as verteporfin or protoporphyrin IX (49,50), were considered to be possible treatments for various cancer types (51,52). The mechanism of action of these medicines is to inhibit the Hippo pathway by altering or disrupting the binding interface of YAP and TEAD (53). In addition, certain studies are aiming to utilize the role of Hippo in tumor immunity to treat non-small cell lung cancer (54) and malignant pleural mesothelioma (55); however, this is a novel area of research and requires further investigation.

A new direction for future cancer treatment has been discovered by studying the crosstalk between Wnt and Hippo. Based on the crosstalk between these two signaling pathways, it has been proposed that overexpression of cytoplasmic YAP may restrict the Wnt signal and thus reduce the proliferation of cancer cells (56,57). Furthermore, aberrant oncogenic Wnt signaling has been demonstrated to be detrimental for the abnormal proliferation of cancer cells, but had no obvious effect on normal stem cells; thus, it is a favorable strategy for future cancer therapy (16). As this mechanism has only been investigated in cells or mouse models, additional research is necessary prior to clinical use.

7. Conclusion

In conclusion, YAP not only serves a role in the Hippo pathway to act as a co-regulator of transcription activity but also acts as a regulator in the Wnt signaling pathway, and knockdown of YAP causes metabolic disorders and results in abnormal organ size. Depending on the cell type, YAP exerts different roles by activating different mechanisms. Nuclear YAP upregulates β-catenin and cytoplasmic YAP negatively modulates the Wnt signaling pathway. As these two signaling pathways are involved in physiological metabolism and homeostasis, YAP may be used as a novel target for the treatment of fibrosis and cancer. While this has been recently investigated in the laboratory, the crosstalk between the Hippo and Wnt signaling pathways is complex and further research is required in the future.

Acknowledgements

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (grant no. 81970978), the Zhejiang Province Natural Science Foundation of China (grant no. LQ18H140004) and the Zhejiang Provincial Medical Health & Hygienic Science and Technology Project of China (grant nos. 2018256920 and 2019RC156).

Availability of data and materials

Not applicable.

Authors' contributions

LJ and JuaL conceived and designed the study. LJ, CZ and YS searched the literature and drafted the manuscript. JuaL and JunL critically revised the manuscript for important intellectual content. All authors read and approved the final 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.

References

1. Panciera T, Azzolin L, Fujimura A, Di Biagio D, Frasson C, Bresolin S, Soligo S, Basso G, Bicciato S, Rosato A, *et al*: Induction of expandable tissue-specific stem/progenitor cells through transient expression of YAP/TAZ. Cell Stem Cell 19: 725-737, 2016.

2. Mauviel A, Nallet-Staub F and Varelas X: Integrating developmental signals: A Hippo in the (path)way. Oncogene 31: 1743-1756, 2012.
3. Nishioka N, Inoue K, Adachi K, Kiyonari H, Ota M, Ralston A, Yabuta N, Hirahara S, Stephenson RO, Ogonuki N, *et al*: The Hippo signaling pathway components Lats and Yap Pattern TEAD4 activity to distinguish mouse trophectoderm from inner cell mass. Dev Cell 16: 398-410, 2009.
4. Xin M, Kim Y, Sutherland LB, Murakami M, Qi X, McAnally J, Porrello ER, Mahmoud AI, Tan W, Shelton JM, *et al*: Hippo pathway effector Yap promotes cardiac regeneration. Proc Natl Acad Sci USA 110: 13839-13844, 2013.
5. Stampouloglou E and Varelas X: Phosphatidic acid signals via the Hippo pathway. Mol Cell 72: 205-206, 2018.
6. Zhao B, Ye X, Yu J, Li L, Li W, Li S, Yu J, Lin JD, Wang CY, Chinnaiyan AM, *et al*: TEAD mediates YAP-dependent gene induction and growth control. Genes Dev 22: 1962-1971, 2008.
7. Heallen T, Zhang M, Wang J, Bonilla-Claudio M, Klysik E, Johnson RL and Martin JF: Hippo pathway inhibits Wnt signaling to restrain cardiomyocyte proliferation and heart size. Science 332: 458-461, 2011.
8. Varelas X, Miller BW, Sopko R, Song S, Gregorieff A, Fellouse FA, Sakuma R, Pawson T, Hunziker W, McNeill H, *et al*: The Hippo pathway regulates Wnt/β-catenin signaling. Dev Cell 18: 579-591, 2010.
9. Zhuang J, Lin S, Dong L, Cheng K and Weng W: Magnetically actuated mechanical stimuli on Fe_3O_4/mineralized collagen coatings to enhance osteogenic differentiation of the MC3T3-E1 cells. Acta Biomater 71: 49-60, 2018.
10. Zhuang J, Lin S, Dong L, Cheng K and Weng W: Magnetically assisted electrodeposition of aligned collagen coatings. ACS Biomater Sci Eng 4: 5, 2018.
11. Regimbald-Dumas Y and He X: Wnt signalling: What the X@# is WTX? EMBO J 30: 1415-1417, 2011.
12. MacDonald BT, Tamai K and He X: Wnt/β-Catenin signaling: Components, mechanisms, and diseases. Dev Cell 17: 9-26, 2009.
13. Sebastian R, Michael SK, Katerina G, Sanjay K and David VS: Dynamics of mechanosensitive neural stem cell differentiation. Stem Cells 35: 497-506, 2017.
14. Li Z, Zhao B, Wang P, Chen F, Dong Z, Yang H, Guan KL and Xu Y: Structural insights into the YAP and TEAD complex. Genes Dev 24: 235-240, 2010.
15. Imajo M, Miyatake K, Iimura A, Miyamoto A and Nishida E: A molecular mechanism that links Hippo signalling to the inhibition of Wnt/β-catenin signalling. EMBO J 31: 1109-1122, 2012.
16. Azzolin L, Panciera T, Soligo S, Enzo E, Bicciato S, Dupont S, Bresolin S, Frasson C, Basso G, Guzzardo V, *et al*: YAP/TAZ incorporation in the β-catenin destruction complex orchestrates the Wnt response. Cell 158: 157-170, 2014.
17. Wang J and Martin JF: Hippo pathway: An emerging regulator of craniofacial and dental development. J Dent Res 96: 1229-1237, 2017.
18. Deng F, Peng L, Li Z, Tan G, Liang E, Chen S, Zhao X and Zhi F: YAP triggers the Wnt/β-catenin signalling pathway and promotes enterocyte self-renewal, regeneration and tumorigenesis after DSS-induced injury. Cell Death Dis 9: 153, 2018.
19. Sansom OJ, Griffiths DF, Reed KR, Winton DJ and Clarke AR: Apc deficiency predisposes to renal carcinoma in the mouse. Oncogene 24: 8205-8210, 2005.
20. Saadi-Kheddouci S, Berrebi D, Romagnolo B, Cluzeaud F, Peuchmaur M, Kahn A, Vandewalle A and Perret C: Early development of polycystic kidney disease in transgenic mice expressing an activated mutant of the beta-catenin gene. Oncogene 20: 5972-5981, 2001.
21. Dupont S, Morsut L, Aragona M, Enzo E, Giulitti S, Cordenonsi M, Zanconato F, Le Digabel J, Forcato M, Bicciato S, *et al*: Role of YAP/TAZ in mechanotransduction. Nature 474: 179-183, 2011.
22. Kuroda M, Wada H, Kimura Y, Ueda K and Kioka N: Vinculin promotes nuclear localization of TAZ to inhibit ECM stiffness-dependent differentiation into adipocytes. J Cell Science 130: 989-1002, 2017.
23. Papaspyropoulos A, Bradley L, Thapa A, Leung CY, Toskas K, Koennig D, Pefani DE, Raso C, Grou C, Hamilton G, *et al*: RASSF1A uncouples Wnt from Hippo signalling and promotes YAP mediated differentiation via p73. Nat Commun 9: 424, 2018.
24. Park HW, Kim YC, Yu B, Moroishi T, Mo JS, Plouffe SW, Meng Z, Lin KC, Yu FX, Alexander CM, *et al*: Alternative Wnt signaling activates YAP/TAZ. Cell 162: 780-794, 2015.
25. Liu H, Du S, Lei T, Wang H, He X, Tong R and Wang Y: Multifaceted regulation and functions of YAP/TAZ in tumors (Review). Oncol Rep 40: 16-28, 2018.
26. Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, Xie J, Ikenoue T, Yu J, Li L, *et al*: Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes Dev 21: 2747-2761, 2007.
27. Tsutsumi R, Masoudi M, Takahashi A, Fujii Y, Hayashi T, Kikuchi I, Satou Y, Taira M and Hatakeyama M: YAP and TAZ, Hippo signaling targets, act as a rheostat for nuclear SHP2 function. Dev Cell 26: 658-665, 2013.
28. Takahashi A, Tsutsumi R, Kikuchi I, Obuse C, Saito Y, Seidi A, Karisch R, Fernandez M, Cho T, Ohnishi N, *et al*: SHP2 tyrosine phosphatase converts parafibromin/cdc73 from a tumor suppressor to an oncogenic driver. Mol Cell 43: 45-56, 2011.
29. Pan J, Xiong L, Zhao K, Zeng P, Wang B, Tang FL, Sun D, Guo HH, Yang X, Cui S, *et al*: YAP promotes osteogenesis and suppresses adipogenic differentiation by regulating β-catenin signaling. Bone Res 6: 18, 2018.
30. Yang B, Sun H, Song F, Yu M, Wu Y and Wang J: YAP1 negatively regulates chondrocyte differentiation partly by activating the β-catenin signaling pathway. Cell 87: 104-113, 2017.
31. Zhao K, Shen C, Lu Y, Huang Z, Li L, Rand CD, Pan J, Sun XD, Tan Z, Wang H, *et al*: Muscle Yap is a regulator of neuromuscular junction formation and regeneration. J Neurosci 37: 3465-3477, 2017.
32. Urban ML, Manenti L and Vaglio A: Fibrosis-a common pathway to organ injury and failure. N Engl J Med 373: 95-96, 2015.
33. Henderson WR Jr, Chi EY, Ye X, Nguyen C, Tien YT, Zhou B, Borok Z, Knight DA and Kahn M: Inhibition of Wnt/beta-catenin/CREB binding protein (CBP) signaling reverses pulmonary fibrosis. Proc Natl Acad Sci USA 107: 14309-14314, 2010.
34. Satoh M, Nagasu H, Morita Y, Yamaguchi TP, Kanwar YS and Kashihara N: Klotho protects against mouse renal fibrosis by inhibiting Wnt signaling. Am J Physiol Renal Physiol 303: F1641-F1651, 2012.
35. Wang M, Chen DQ, Chen L, Liu D, Zhao H, Zhang ZH, Vaziri ND, Guo Y, Zhao YY and Cao G: Novel RAS inhibitors poricoic acid ZG and poricoic acid ZH attenuate renal fibrosis via a Wnt/β-catenin pathway and targeted phosphorylation of smad3 signaling. J Agric Food Chem 66: 1828-1842, 2018.
36. Noguchi S, Saito A and Nagase T: YAP/TAZ signaling as a molecular link between fibrosis and cancer. Int J Mol Sci 19: 3674, 2018.
37. Haak AJ, Kostallari E, Sicard D, Ligresti G, Choi KM, Caporarello N, Jones DL, Tan Q, Meridew J, Diaz Espinosa AM, *et al*: Selective YAP/TAZ inhibition in fibroblasts via dopamine receptor D1 agonism reverses fibrosis. Sci Transl Med 11: eaau6296, 2019.
38. Toyama T, Looney AP, Baker BM, Stawski L, Haines P, Simms R, Szymaniak AD, Varelas X and Trojanowska M: Therapeutic targeting of TAZ and YAP by dimethyl fumarate in systemic sclerosis fibrosis. J Invest Dermatol 138: 78-88, 2018.
39. Zhu H, Ge T, Pan Y and Zhang S: Advanced role of Hippo signaling in endometrial fibrosis: Implications for intrauterine adhesion. Chin Med J (Engl) 130: 2732-2737, 2017.
40. Verma S, Yeddula N, Soda Y, Zhu Q, Pao G, Moresco J, Diedrich JK, Hong A, Plouffe S, Moroishi T, *et al*: BRCA1/BARD1-dependent ubiquitination of NF2 regulates Hippo-YAP1 signaling. Proc Natl Acad Sci USA 116: 7363-7370, 2019.
41. Zanconato F, Forcato M, Battilana G, Azzolin L, Quaranta E, Bodega B, Rosato A, Bicciato S, Cordenonsi M and Piccolo S: Genome-wide association between YAP/TAZ/TEAD and AP-1 at enhancers drives oncogenic growth. Nat Cell Biol 17: 1218-1227, 2015.
42. Moya IM and Halder G: Hippo-YAP/TAZ signalling in organ regeneration and regenerative medicine. Nat Rev Molr Cell Biol 20: 211-226, 2019.
43. Sulaiman A, McGarry S, Li L, Jia D, Ooi S, Addison C, Dimitroulakos J, Arnaout A, Nessim C, Yao Z, *et al*: Dual inhibition of Wnt and Yes-associated protein signaling retards the growth of triple negative breast cancer in both mesenchymal and epithelial states. Mol Oncol 12: 423-440, 2018.
44. Hu J, Gao C, Chen G and Gao X: Abstract LB-310: PYK2 as a therapeutic target for pancreatic cancer. Cancer Res 77: 310, 2017.

45. Szalmás A, Tomaić V, Basukala O, Massimi P, Mittal S, Kónya J and Banks L: The PTPN14 tumor suppressor is a degradation target of human papillomavirus E7. J Virol 91: e00057-00017, 2017.
46. Tao J, Calvisi DF, Ranganathan S, Cigliano A, Zhou L, Singh S, Jiang L, Fan B, Terracciano L, Armeanu-Ebinger S, *et al*: Activation of β-Catenin and Yap1 in human hepatoblastoma and induction of hepatocarcinogenesis in mice. Gastroenterology 147: 690-701, 2014.
47. Rosenbluh J, Nijhawan D, Cox AG, Li X, Neal JT, Schafer EJ, Zack TI, Wang X, Tsherniak A, Schinzel AC, *et al*: β-catenin-driven cancers require a YAP1 transcriptional complex for survival and tumorigenesis. Cell 151: 1457-1473, 2012.
48. Kartha VK, Alamoud KA, Sadykov K Nguyen BC, Laroche F, Feng H, Lee J, Pai SI, Varelas X, Egloff AM, *et al*: Functional and genomic analyses reveal therapeutic potential of targeting β-catenin/CBP activity in head and neck cancer. Genome Med 10: 54, 2018.
49. Santucci M, Vignudelli T, Ferrari S, Mor M, Scalvini L, Bolognesi ML, Uliassi E and Costi MP: The Hippo pathway and YAP/TAZ-TEAD protein-protein interaction as targets for regenerative medicine and cancer treatment. J Med Chem 58: 4857-4873, 2015.
50. Liu-Chittenden Y, Huang B, Shim JS, Chen Q, Lee SJ, Anders RA, Liu JO and Pan D: Genetic and pharmacological disruption of the TEAD-YAP complex suppresses the oncogenic activity of YAP. Genes Dev 26: 1300-1305, 2012.
51. Rozengurt E, Sinnett-Smith J and Eibl G: Yes-associated protein (YAP) in pancreatic cancer: At the epicenter of a targetable signaling network associated with patient survival. Signal Transduct Target Ther 3: 11, 2018.
52. Stampouloglou E, Cheng N, Federico A, Slaby E, Monti S, Szeto GL and Varelas X: Yap suppresses T-cell function and infiltration in the tumor microenvironment. PLoS Biol 18: e3000591, 2020.
53. Crawford JJ, Bronner SM and Zbieg JR: Hippo pathway inhibition by blocking the YAP/TAZ-TEAD interface: A patent review. Expert Opin Ther Pat 28: 867-873, 2018.
54. Hsu PC, Jablons DM, Yang CT and You L: Epidermal growth factor receptor (EGFR) pathway, Yes-associated protein (YAP) and the regulation of programmed death-ligand 1 (PD-L1) in non-small cell lung cancer (NSCLC). Int J Mol Sci 20: 3821, 2019.
55. Hsu PC, Yang CT, Jablons DM and You L: The role of Yes-associated protein (YAP) in regulating programmed death-ligand 1 (PD-L1) in thoracic cancer. Biomedicines 6: 114, 2018.
56. Alam M, Bouillez A, Tagde A, Ahmad R, Rajabi H, Maeda T, Hiraki M, Suzuki Y and Kufe D: MUC1-C represses the crumbs complex polarity factor CRB3 and downregulates the Hippo pathway. Mol Cancer Res 14: 1266-1276, 2016.
57. Moroishi T, Hansen CG and Guan KL: The emerging roles of YAP and TAZ in cancer. Nat Rev Cancer 15: 73-79, 2015.