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New Insights into the Roles of Yes-Associated Protein (YAP1) in Colorectal Cancer Development and Progression

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Abstract

Yes-associated protein (YAP1), the downstream effector of the Hippo pathway, plays important roles in the regulation of tissue reconstruction, stem cell proliferation, and development of different cancers. The regulation of YAP1 phosphorylation, YAP1 expression level, and its cellular localization have been considered in cancer development. There are different experimental evidences that indicate that YAP1 activation results in tumorigenesis, tumor progression, and metastasis. YAP1 is a transcription co-activator, and its dysregulation has been suggested in various cancers including colorectal cancer (CRC). The localization of YAP1 in the nucleus results in YAP1 interactions with different transcription factors to promote the expression of genes involved in cell proliferation, metastasis, and stem cell maintenance. However, a number of studies have been reported the tumor suppressor role of YAP1 in CRC. Therefore, a better understanding of the YAP1 regulation could be helpful for prevention, diagnosis, and treatment of CRC. In this review, we will discuss different roles of YAP1 in CRC progression through the regulatory roles of long non-coding RNAs (LncRNAs), microRNAs (miRNAs) and circular RNAs (CircRNAs) in YAP1 regulation.

Keywords: YAP1, Colorectal Cancer, Hippo Pathway, LncRNAs, miRNAs, circRNAs

1. Context

CRC is one of the most prevalent cancers with nearly two million new cases each year across the globe. CRC is known as the third most common cancer and the forth cause of cancer-related death (700000 deaths per year, globally). Personal characteristics or habits like age and sex, the history of chronic disease, family history and lifestyle are identified as CRC risk factors. CRC is the second most common cancer in women (9.2%) and the third most common in men (10%). Several cases of CRC have been diagnosed in western countries (55%), but this tendency is changing due to the fast development of a number of countries in recent years (1). CRC-related genes are mostly involved in cell growth, survival, adhesion, invasion, and angiogenesis (2). However, a better understanding of important genes involved in creating oncogenic phenotype and also molecular events supporting tumor development can undoubtedly help to discover more efficient drugs to prevent CRC (3). There is the relative survival of 5 years only in 8% of the advanced CRC patients. Despite the developments of chemotherapy strategies and surgery for CRC treatment, CRC is still the third cause of death worldwide. The molecular mechanisms involved in CRC tumorigenesis and tumor development are complicated (4). Therefore, discovering new prognostic markers and new regulatory mechanisms involved in CRC could help to develop new effective therapeutic targets.

The Hippo signaling pathway is identified as a key pathway in the pathogenesis of colorectal cancer. Hippo is a highly protected tumor suppressor pathway with important roles in organ size through the regulation of apoptosis and cell proliferation (3). Previous studies indicate that dysregulation of the Hippo pathway is involved in CRC development. Many studies highlight the role of YAP1 as one of the most important Hippo pathway genes in the development and progression of CRC. The overexpression of Yap1 has been reported in CRC patients compared with controls. YAP1 has also been considered as a prognostic factor for general survival in CRC patients. However, a number of recent studies show that YAP1 can be a tumor suppressor because it can suppress the tumorigenesis of CRC by affecting cell growth, apoptosis, maintenance of stem cells, and inflammatory responses. Both oncogenic and tumor suppressor activity of YAP1 in CRC have been suggested in previous studies (5, 6). Hence, understanding the role of YAP1 and its regulatory mechanisms could be important in prevention, recognition and treatment of CRC (7).

2. Molecular Structures of Hippo Pathway

The Hippo pathway was originally discovered in drosophila, before later being identified in mammals. It has been shown that the Hippo pathway is involved in different diseases through controlling the organ size, maintaining tissue homeostasis and regeneration, and directing stem cell differentiation and renewal, tumorigenesis development, drug-resistance and metastasis (5, 8, 9). Dysregulation of Hippo pathway has been reported in various human cancers including lung, liver, ovarian, and colorectal cancers (10). The loss of function mutations in core members of Hippo pathway including *Warts*, *Salvador*, *Mob-as-tumor suppressor* or *Hippo* (HPO) significantly cause the excessive tissue-specific growth of developing tissues. Yorkie (YKI), homologous to Drosophila YAP1 and TAZ, are considered as the downstream effectors of the Hippo pathway in Drosophila. In vertebrates, both the Hippo pathway and YAP1 regulation are highly protected. Generally, YAP1 and TAZ are phosphorylated and repressed by kinase cascades of the Hippo pathway. In more details, LATS1 and LATS2, which are protein kinases homologous to Drosophila Warts (Wts), are activated by association with the Mps one binder kinase activator-like 1A (MOBKL1A) and 1B (MOBKL1B). MOBKL1A and MOBKL1B are homologues of Drosophila mob. LATS kinases are also activated by phosphorylation of STE20 family protein kinases MST1 and MST2, which are homologues of Hippo (Hpo) in Drosophila. MOB1 is also phosphorylated by MST, which results in enhanced MOB1-LATS interactions. MST is activated by the binding of Salvador (Sav1), a homologue of Sav in Drosophila. LATS/MOB complex can then bind to YAP1/TAZ and phosphorylate them in order to prevent nuclear transfer or to develop protein degradation. It has been reported that LATS can phosphorylate YAP1 in five distinct serine residues. Most of the repression related to LATS in YAP1 and TAZ is regulated by two serine. The phosphorylation of YAP in serine 127 or TAZ in serine 89 results in the development of 14 - 3 - 3 binding and cytoplasmic sequestration (11). The phosphorylation of serine 381 in YAP1 or serine 311 in TAZ also induce the next phosphorylation by casein kinase I S/E. The phosphorylation results in the utilization of E3 ubiquitin ligase SCF (-TRCP), leading to proteasome ubiquitination and degradation (12).

Furthermore, the Hippo pathway is inactivated through different regulatory factors including mechanical cues, cell polarity, biochemical factors, cellular energy stress, growth factors, and G-protein-coupled receptor (GPCRs). Therefore, the inactivation of this pathway results in activation of YAP1 and translocation of this co-activator from the cytosol to the nucleus. Both YAP1 and TAZ do not have DNA binding domains, needing to interact with other transcription factors to induce transcription. Members of the TEA family (TEADs1-4) comprise a group of transcription factors that regulate the expression of diverse genes related to cell proliferation, differentiation, and apoptosis. In mammals, transcription factors of the TEAD family are identified as partners of YAP1. Recently, the role of TEAD proteins in tumorigenesis and oncogenic functioning in various malignancies was confirmed (13). TEAD1-4 control the expression of a large group of different genes including FGF1, CYR61 and CTGF, which play roles in cell growth, survival and migration (Figure 1) (14). Liu reported that the nucleus expression of TEAD4 can be used as a biomarker for CRC development and prognosis. TEAD4 regulates YAP1 by direct connection and transcription activation (15).

3. The Regulation of YAP1 and Crosstalk of YAP1 with Other Pathways in CRC Progression

YAP1 is a transcription co-activator that is dysregulated by the Hippo pathway. In 1994, YAP1 was identified and cloned as a protein that accompanies the SRC family of non-receptor tyrosine kinases. This protein was recognized as the key regulator of early embryonic development and also development and growth of several types of tissues. YAP1 also plays important roles in mature organs, especially in tissue repair and regeneration. Abnormally low YAP1 activity may result in developmental defects, tissue atrophy and incomplete tissue repair. While undoubtedly, high activity of YAP1 results in increasing tissue growth, tumor formation, cancer progression and metastasis. Moreover, evidence show that in addition to tumor growth, YAP1 activation plays a direct role in metastasis of a wide variety of cancers including, melanoma, lung cancer, breast cancer, cholangiocarcinoma, gastric cancer, ovarian cancer, squamous cell carcinoma and colorectal cancer. Inversely, a number of studies indicate that YAP1 activation can repress metastasis. Therefore, YAP1 activation results in progression of metastasis in many cancers, but probably not in all of them (12). A long and growing list of proteins and pathways that regulate YAP1 in response to a different set of extracellular and mechanical cues have been reported in previous studies (12). Many of these pathways regulate YAP1 activity independent of the Hippo pathway. Hippo/YAP1 regulates many biological and pathological features including the size of the organ, tissue homeostasis, cell proliferation, apoptosis and tumorigenesis by crosstalk with other signaling pathways (6). Crosstalk of Hippo pathway with other signaling pathways is highly dependent on the important roles of YAP1, which is regulated by upstream signal molecules and can regulate a set of targets through interaction with transcription factors. Here, we discuss the important crosstalk between YAP1 and other pathways, which plays a role in CRC progression. Yang

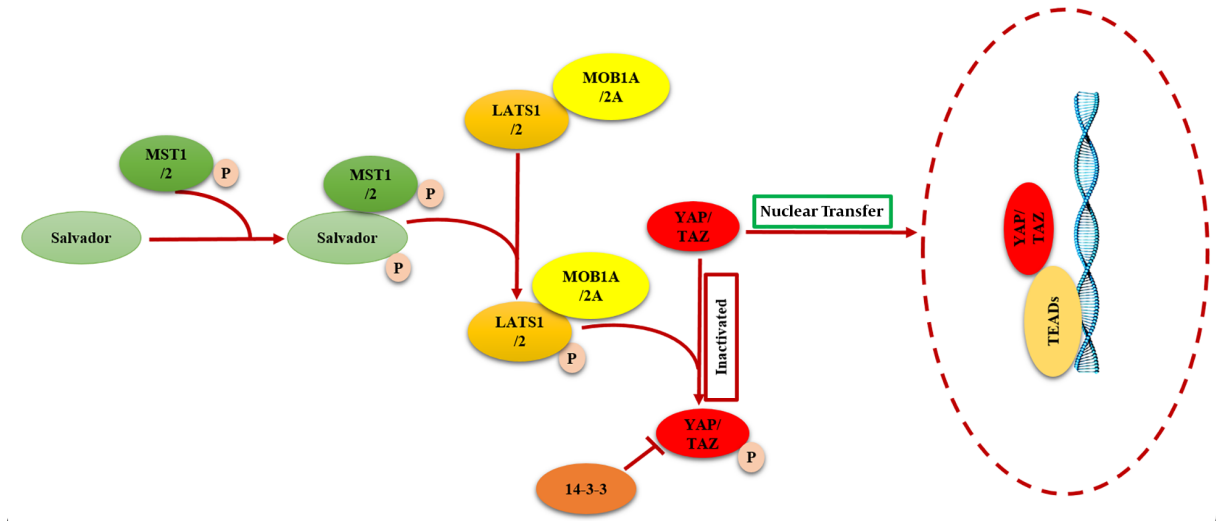

Figure 1. Schematic diagram of the Hippo pathway in mammals

et al. showed that YAP1 downregulates PTEN expression by induction of miR29, which represses PTEN translation. They also found that expression levels of YAP1 and PTEN in CRC-derived cell lines induce myeloid-derived suppressor cells (MDSCs) in CRC. YAP1 results in the induction of CRC-derived MDSC through suppressing PTEN expression. These findings suggest that YAP1 and PTEN act in tumor development by promoting pro-tumorigenic MDSCs in addition to their oncogenic role in CRC. MDSC population spreads in peripheral blood and tumor tissues of CRC patients. It has been shown that MDSCs inhibit T-cell proliferation and promote CRC cell growth in vitro (16). RASAL2 has also been identified as a regulatory protein for YAP1 activity. The increased expression level of RASAL2, a member of the RAS GAP family, has been demonstrated in CRC. This molecule targets LATS2/YAP1, which results in YAP1 dephosphorylation and transfer to the nucleus where regulation of the YAP1 target genes occurs (3). GPRC5A is an hypoxia-induced protein that protects cells from apoptosis during reductions in oxygen. GPRC5A maintains CRC cells facing hypoxic conditions by activating the YAP1 effector in the Hippo pathway and in BCL2L1, making it an anti-apoptotic target gene. HIF acts as a direct transcription activator of GPRC5A. So, YAP1 is an important downstream effector of HIF, which results in HIF-driven, GPRC5A-dependent cell survival (17).

HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1 (HACE1) has also been identified as a tumorigenesis inhibitor that is downregulated in several types of cancers. It was reported that HACE1 reduces CRC growth and metastasis through the Hippo pathway. HACE1 silencing results in upregulation of YAP1 as well as its downstream target genes including CYr61 and CTGF (4).

In another study, Haijunli et al. showed that mitochondrial divisions act as a regulator of the Hippo pathway in the tumorigenesis of rectal cancer (RC) and metastasis. High expression of YAP1 results in dephosphorylation of JNK. The inactivated form of JNK blocks DrP1 and mitochondrial division. Therefore, YAP1 maintains the structure and function of the mitochondria, reduces HtrA2/omi emission, and inhibits cell apoptosis. HtrA2/omi inhibition maintains F-action balance and lamellipodium formation through cofilin modification, leading to the development of RC migration and invasion. The WW domain (amino acids 102 - 263) in YAP1 is essential for interaction with JNK. It should be noted that YAP1 phosphorylation has no effect on its interaction with JNK. Therefore, YAP1 probably regulates RC survival and migration independent of its phosphorylation. Indeed, YAP1 nuclear localization probably has a small role in cancer development (Figure 2).

Some other studies confirm that YAP1 level is sufficiently related to the target gene expression and is significantly associated with cancer progression. At the same time, several studies show that YAP1 has the ability of interaction with tumor suppressors in the cytoplasm, supporting the idea that overexpression of YAP1 is an important factor in tumorigenesis without considering nuclear localization or keeping YAP1 in the cytoplasm (18). Generally, as the Hippo pathway does not have any plasma membrane receptor or extracellular ligand, it is not clear how YAP1 is activated in oncogenic pathways in CRC. Hence, recognition of the crosstalk between different signaling pathways and

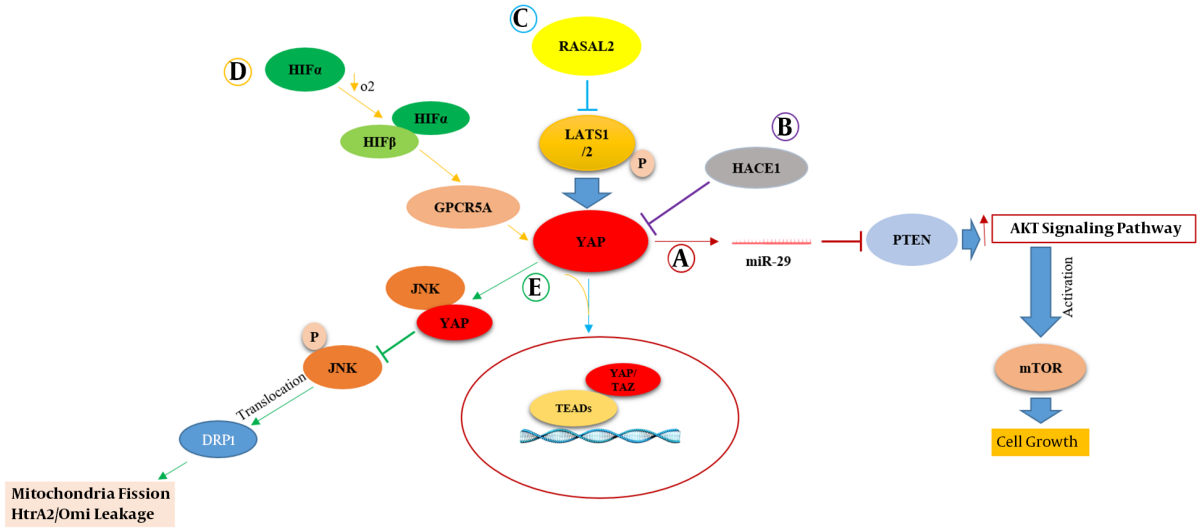

Figure 2. The regulation of YAP1 and crosstalk of YAP1 with other pathways in CRC progression

the Hippo pathway is significant. YAP1 usually acts as an oncogene, but some studies support the idea that YAP1 acts as a tumor suppressor in cancers such as head and neck cancers (HNC), breast cancer, hematological cancers and CRC. The double role of YAP1 in CRC cells has been studied in detail in a previous study (6).

4. Non-Coding RNAs

Non-coding RNAs (NcRNAs) regulate gene expression through epigenetic modifications, and can be disrupted in cancers (19). NcRNAs are also identified to have oncogenic or tumor suppressor roles in various cancer types including CRC (20). In this review, among different kinds of ncRNAs, the role of LncRNAs, miRNAs and circRNAs specifically in YAP1 regulation will be discussed (Figure 3).

5. MiRNAs and YAP1 in CRC Development

MiRNAs are a group of approximately 19 - 25 nt RNAs that regulate post-transcriptional expression of transcripts by binding to their 3' untranslated region (3' UTR) and inhibiting their translation (21, 22). Overexpression of oncomiRs or decreased expression of tumor suppressor miRNAs are associated with various human cancers (22). These molecules are considered as novel biomarkers for diagnosis, prognosis and cure of CRC (23). Previous studies reported miRNAs that are related to CRC, especially by targeting YAP1.

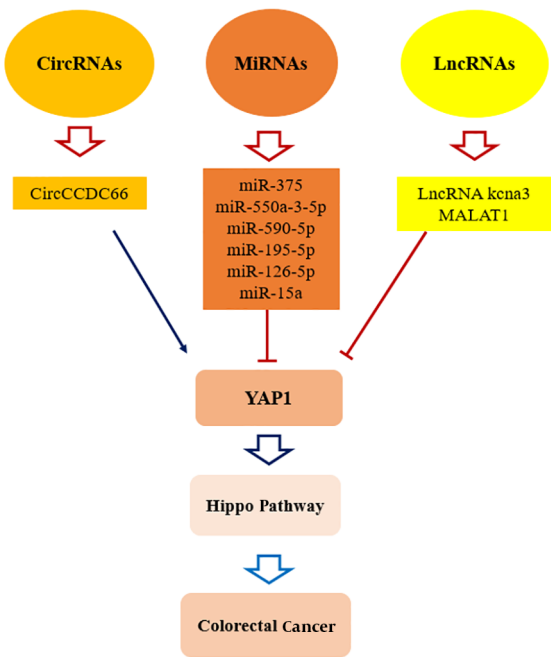

Figure 3. Regulatory roles of lncRNAs, miRNAs and circRNAs in CRC progression by targeting YAP1. Positive regulation is shown by blue arrows and negative regulation is illustrated by red lines.

In CRC, YAP1 is a direct target of miR-375. MiR-375 decreases tumor growth by inducing apoptosis, and is dysregulated in both CRC cell lines and clinical samples. This

pro-apoptotic role of miR-375 seems to be mediated by targeting YAP1 and its anti-apoptotic downstream target genes including BIRC5 and BCL2L (24). This miRNA is also downregulated in both plasma and tissues of CRC patients and could discriminate CRC patients from healthy controls in plasma samples (25). MiR-550a-3-5p suppresses the proliferation and metastasis of cells and also tumor sphere formation through direct targeting of YAP1 in many cancer cell types. There is an inverse correlation between YAP1 and miR-550a-3-5p in colon cancer tissues, which is regulated by density dependent culture. Hence, it has been suggested that the elevated expression of YAP1 suppresses miRNA biogenesis by this manner (21).

miRNA biogenesis could be activated by cell-cell contact, and YAP1 regulates this process through a cell-density depended way (26, 27). In CRC cells, miR-590-5p directly targets YAP1 and prohibits tumorigenesis; increasing cancer cell density leads to elevated expression of DICERI, increased miR-590 biogenesis, and inhibited YAP1 expression (15). It was also indicated that miR-195-5p targets the 3'-UTR of YAP1. The downregulation of YAP1 through miR-195-5p resulted in decreased tumor development in a mouse xenograft model for CRC. Indeed, this miRNA was suggested as a prognostic marker for predicting the outcome of CRC patients (28).

Recently, a regulatory mechanism of the YAP1-MALAT1-miR-126-5p axis has been reported in CRC. In this regulatory Gene-LncRNA-miRNA axis, YAP1-induced MALAT1 promotes the expression of TWIST, VEGFA and SLUG by sponging miR-126-5p in CRC. TWIST, VEGFA and SLUG are identified as metastasis-associated molecules. Thus, these results suggest that the YAP1-MALAT1-miR-126-5p axis could regulate epithelial–mesenchymal transition and angiogenesis in CRC. This regulatory mechanism could provide probable biomarkers and therapeutic targets for CRC therapy (29). It was also demonstrated that miR-15a could be a potential therapeutic target in CRC as it inhibits several important genes including BCL2, BMI1, YAP1 and DCLK1 (30).

6. LncRNAs and YAP1 in CRC

LncRNAs are a group of non-coding RNAs with a length of 200 nt up to 100 kb, and lack a significant open reading frame. These molecules are dysregulated in numerous cancers, which highlights their role as oncogenic or tumor suppressor factors (31). LncRNAs participate in regulation of gene expression through various mechanisms including transcriptional and post- transcriptional regulation as well as epigenetic modifications (32). Previous studies show the association of CRC-related LncRNAs with different biological processes involved in disease progression, such as cell proliferation, apoptosis, and invasion (33). In CRC, LncRNA kcna3 suppresses migration, invasion, proliferation and carcinogenesis by downregulation of YAP1 expression, which suggests LncRNA kcna3/YAP1 as a prognostic marker and therapeutic target for this disease (34).

7. CircRNAs and YAP1 in CRC

CircRNAs are a group of non-coding RNAs that are formed by covalent binding between the 3' and 5' ends of phosphodiester bonds, leading to a loop structure. The aberrant expression of these molecules has close a relation with proliferation and metastasis of tumor cells (35). CircCCDC66 develops colorectal cancer through several pathological processes including tumor growth and metastasis. The expression level of YAP1 is significantly upregulated through CircCCDC66 overexpression. It is suggested that CircCCDC66 may protect several oncogenes from the attack of miRNAs including YAP1, with these genes having a positive correlation with colon cancer (36).

8. Conclusions

The fast progress of the Hippo pathway investigation in the last years has built a road map of Hippo and its regulatory roles in tumorigenesis. The critical roles of this pathway in CRC has been reported in different studies. Although the role of YAP1 as the downstream effector of the Hippo pathway in CRC has been well studied, more details need to be discussed. Many studies have suggested YAP1 as an oncogene in CRC. However, there are recent findings that suggest YAP1 as a tumor suppressor in CRC. In this review, we comprehensively summarized all new research regarding the molecular mechanisms of YAP1, particularly in CRC development. Altogether, YAP1 is regulated at different levels including miRNA, lncRAN and CircRNA regulatory mechanisms. Further studies about the molecular mechanisms responsible for the function of YAP1 could be helpful in the early diagnosis, prevention and therapy of CRC.

Footnotes

Authors' Contribution: Conception and design of the study: Fariba Dehghanian and Zohreh Hojati; collection and assembly of data, interpretation and manuscript writing: Fariba Dehghanian, Zahra Azhir, and Atefeh Akbari; interpretation and final approval of the manuscript: Zohreh Hojati.

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