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Role of Yes-associated protein [YAP]- A Key Hippo Component in the Onset and Progression of Oral Squamous Cell Carcinoma

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Abstract

Background: Tumorigenesis is an abnormal growth of cells within the body, usually induced by abnormal proliferation of the stem cells or abnormal apoptosis, the usual disturbance in the cell cycle. Various signalling pathways play a role in the cell cycle, which, when altered, result in abnormal cell proliferation and thus cancerogenesis. One such important pathway is the Hippo pathway, which plays a major role in controlling the organ's size. Dysregulation in the components of the hippo pathway, causing cancers, has been studied in the literature in various cancers such as breast cancer, liver cancer, colorectal cancer, and liver cancer.

Aim: This review focuses on the role of Yes-associated protein (YAP), a key effector of the Hippo pathway, in the onset and progression of oral squamous cell carcinoma (OSCC). We summarize recent achievements in understanding YAP's mechanisms in OSCC pathogenesis and discuss its potential as a therapeutic target.

Methods: A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science for articles published between January 2010 and March 2025, using the terms "YAP," "Yes-associated protein," "Hippo pathway," "oral squamous cell carcinoma," and "oral cancer." Inclusion criteria were original research and review articles in English focusing on YAP in OSCC or oral precancerous lesions. Exclusion criteria included non-English articles, case reports, and studies not involving OSCC or YAP.

Conclusions: YAP plays a vital role in malignant transformation, with its dysfunction initiating tumor growth factor expression and being associated with tumor growth and metastasis in OSCC. Understanding YAP's role in the onset and progression of OSCC may identify specific targets for anti-cancer therapy.

Keywords: Hippo pathway, oral cancer, TEAD, wts, yes-associated protein

Introduction

Head and neck cancer is one of the sixth most common cancers worldwide. Over 90% of head and neck cancers are squamous cell carcinomas (HNSCCs), which primarily originate in the larynx, pharynx, and mouth cavity.[1] However, this review specifically focuses on oral squamous cell carcinoma (OSCC), which accounts for the majority of oral malignancies. There were 377,713 documented cases of OSCC (Oral squamous cell carcinoma) in 2020. By 2040, there is expected to be a 40% increase in incidence and a corresponding rise in mortality.[1] A dysregulated tumor microenvironment, epigenetic modifications, and genetic changes all play a part in the intricate and multifaceted process of OSCC development.[2] Comprehending the mechanisms that underlie malignancies of the OSCC is essential to uncover prognostic and therapeutic factors that may enhance the effectiveness of treatment. OSCC remains incurable even with recent advancements in the identification of various therapeutic targets or immune checkpoint inhibitors. Its pathophysiology is still poorly understood, and there are currently no particular biomarkers to help with diagnosis or course prediction. Mutations and the activation of many signal transduction pathways cause OSCC's high invasiveness and metastatic potential.

The growth and differentiation of tissues and organs are regulated by the Hippo signaling pathway. It also plays a significant role in the development and spread of tumors.[3] It is unknown, still unknown exactly how the Hippo pathway regulates oral cancer. A deeper comprehension of the mechanisms behind oral cancer development and the identification of its distinct clinical subtypes will be possible through the characterization of key proteins engaged in major signaling pathways and the analysis of their interactions. This will make it possible to pinpoint particular biochemical targets for later, more potent therapy.

The Hippo pathway

The Hippo signaling pathway is a highly conserved signaling cascade essential for regulating cell survival, differentiation, and proliferation. First identified in Drosophila melanogaster, it comprises key elements such as MST1/2, LATS1/2, MOB1A/B, SAV1, YAP, TAZ, and TEAD1-4.[4] These elements modulate cell activity in response to upstream signals, including mechanical cues, stress signals, and cell polarity.[5,6] Dysregulation of the Hippo pathway has been linked to cancer development, as well as eye, heart, and pulmonary conditions. Targeting the pathway may offer therapeutic benefits for several disorders.

Main components of the pathway

The Hippo pathway regulates cell growth, proliferation, and organ size. In mammals, it consists of a network of kinases, adaptor proteins, transcriptional coactivators, and transcription factors. MST1/2 (mammalian Ste20-like kinases 1 and 2) serve as the pathway's apical regulators, activated by metabolic shifts, cell-to-cell contact, and mechanical stimuli.[7,8] Downstream, LATS1/2 (Large Tumor Suppressor Kinases 1 and 2) are phosphorylated and activated, facilitated by the adaptor protein SAV1.[9] The transcriptional coactivators YAP and TAZ are then phosphorylated by LATS1/2, leading to their cytoplasmic retention and degradation, which inhibits their ability to bind TEAD transcription factors and enter the nucleus (Figure 1).[10] When the Hippo pathway is inactive, YAP and TAZ accumulate in the nucleus, interact with TEAD, and activate genes supporting cell proliferation, survival, and epithelial-mesenchymal transition (EMT).[11,12] Dysregulation of this pathway is closely linked to the onset and progression of several cancers, including OSCC.[13,14]

Yes-associated protein

The Yes-associated protein (YAP) gene, located on chromosome 11q22, encodes the YAP, a critical downstream effector of the Hippo pathway that regulates tissue growth and cell proliferation. YAP has been connected to tumor growth and progression in OSCC.[15] YAP collaborates with TAZ to manage stem cell self-renewal and control cell proliferation.[16] Recent research indicates that YAP interacts with several signaling pathways, implicating it in the initiation and progression of OSCC. Targeting YAP and its signaling pathways may offer a promising therapeutic approach for OSCC.[17]

Structure of YAP

Yes-associated protein, or YAP, is a 488 amino acid protein that is essential for controlling gene expression programs that support cell transformation, survival, and multiplication. Several important domains make up its structure, such as two WW domains, a PDZ-binding

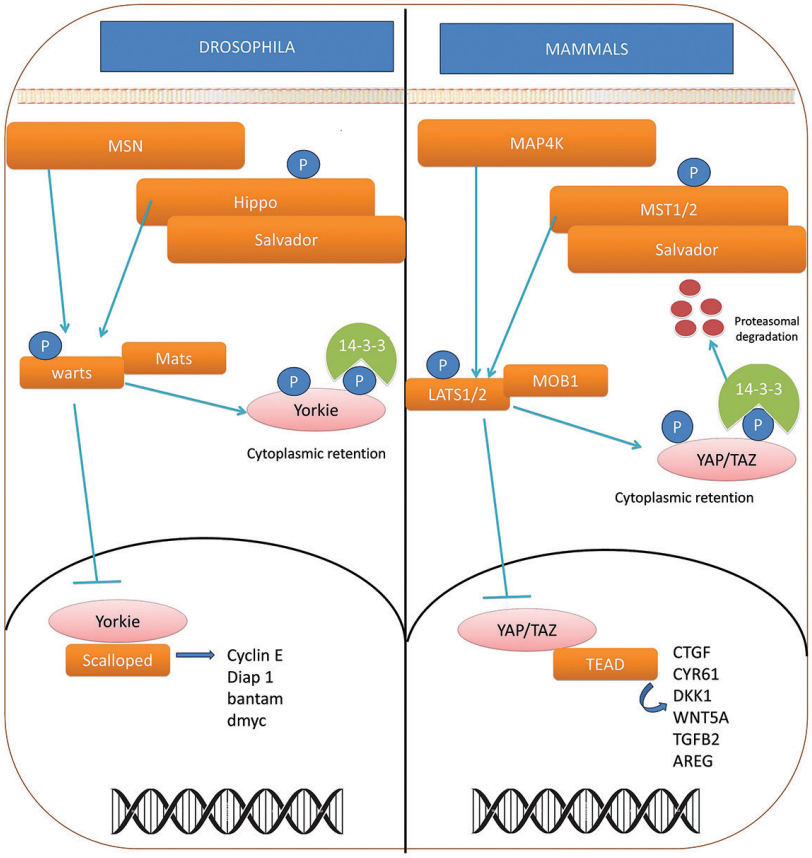

Figure 1: An overview of the Drosophila and mammalian Hippo signaling system. Numerous upstream cues can start hippocampal signaling. Phosphorylation of Warts (LATS1/2) follows Hippo (MST1/2) activation. Yorkie, an effector of the Hippo pathway (YAP/TAZ), is negatively regulated by warts. Yorkie that has not undergone phosphorylation moves into the nucleus, combining with its TEAD transcription factors to enhance the transcription of several genes. On the other hand, when Wts phosphorylates Yorkie, it is sequestered by 14-3-3 proteins in the cytoplasm and eventually degrades.

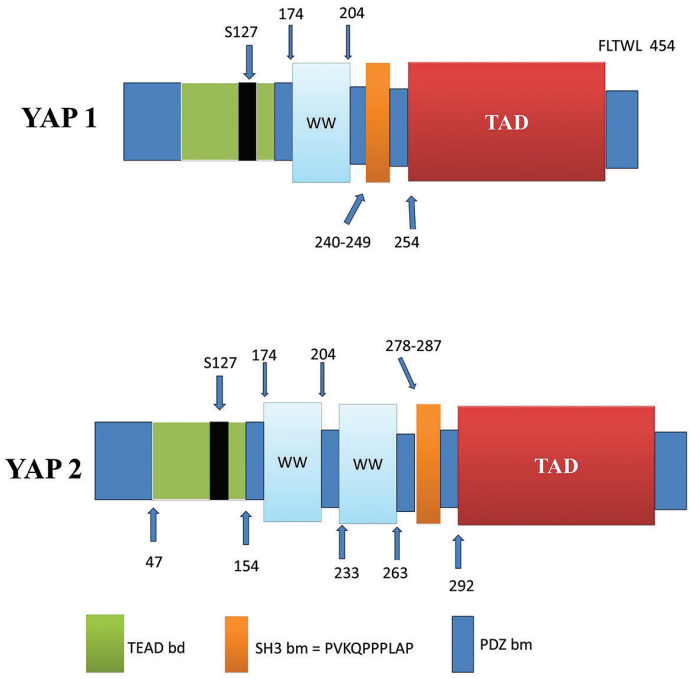

Figure 2: Structure of YAP. The two main YAP protein isoforms' modular architectures. On the scheme of structures, TEAD binding domain (bd), WW domains, transcriptional activation domain (TAD), and SH3 domain-binding motif (bm) are distinguished.

motif, an SH3-binding motif, and a TEAD-binding domain.[18] While the first WW domain also binds to TEAD transcription factors and the second WW domain binds to transcriptional coactivators that interact with PPxY motifs on transcription factors, the TEAD-binding domain enables YAP to bind to the TEAD family of transcription factors (Figure 2).[19] The PDZ-binding motif is necessary for YAP-mediated cellular transformation and is responsible for localizing YAP to particular nuclear foci. Furthermore, in conjunction with the WW1 domain, the SH3-binding motif binds to p53 binding protein 2 to control YAP activity. By binding to and activating different transcription factors through these domains, YAP functions as a transcriptional coactivator, controlling gene expression programs that promote cell division, survival, and growth.[20-21]

Regulation of YAP

Regulation by Hippo pathway:

One important YAP regulator is the Hippo pathway. The proteins MST1/2, LATS1/2, and MOB1 make up this kinase cascade. This mechanism opens up a binding site for 14-3-3 proteins by phosphorylating YAP at Ser127 when it is in an active state. YAP cytoplasmic retention and deactivation result from this. Different cues, including mechanical stress, signaling molecules, and cell-cell interaction, activate the Hippo pathway (Figure 3).[22]

Regulation by phosphorylation and methylation:

The main mechanism that phosphorylation uses is to block YAP activity. Phosphorylation of many locations on YAP can result in its breakdown and exclusion from the nucleus. YAP is phosphorylated at Serine 127 by nuclear Dbf2-related/LATS kinases, which facilitates cytoplasmic localization and destruction of the protein. Consequently, pro-growth genes' transcription is inhibited.[23] Cancer develops when these kinases are artificially depleted. In addition to encouraging the binding of the 14-3-3 protein, phosphorylation of YAP at Serine 127 localizes YAP in the cytoplasm. Moreover, YAP is phosphorylated by Akt kinase, which results in the binding of 14-3-3 protein and the suppression of transcription factors like p53. As a result, when a cell is damaged, pro-apoptotic gene production is suppressed. Protein kinase C η (PKCζ) is another regulator of YAP that phosphorylates YAP at Serine 109 and Threonine 110 to keep it in the cytoplasm. Intestinal stem cells have enhanced tumorigenic and regenerative activity when YAP is deactivated.[24,25]

The function of YAP is also regulated by methylation. Enhancers of zeste (SET)7 and Su(var)3-9 methylate YAP, causing it to become localized in the cytoplasm and preventing it from functioning. To facilitate cytoplasmic localization, phosphorylation at Serine 127 and monomethylation of YAP at Lysine 494 happen simultaneously.[26] Pro-apoptotic gene expression is suppressed and pro-growth gene transcription is inhibited by phosphorylation and methylation, which also promote YAP's cytoplasmic localization and destruction.

YAP regulation by ubiquitination:

YAP is ubiquitinated by E3 ubiquitin ligases like β-TrCP, targeting it for proteasomal degradation. Ubiquitination regulates YAP protein stability and localization. Deubiquitination of YAP by enzymes like USP47 can stabilize YAP and prevent its degradation.[27] Ubiquitination of YAP is often coupled with other post-translational modifications like phosphorylation. Phosphorylation of YAP can create binding sites for E3 ligases, promoting its ubiquitination. Deubiquitinating enzymes like USP47 can counteract ubiquitination and stabilize YAP.[28] The balance between ubiquitination and deubiquitination regulates YAP activity. Dysregulation of YAP ubiquitination and stability is implicated in various cancers. Liu Z *et al*, showed that increased expression of deubiquitinating enzymes like USP47 can stabilize YAP and promote gastric cancer progression.[29] Targeting the ubiquitination-deubiquitination balance of YAP is a potential therapeutic strategy in cancers with YAP activation.

Transcriptional regulation of YAP:

The Ets family transcription factor GABP directly binds to the YAP promoter and increases YAP transcription, especially in oxidative stress conditions. Through its binding to recognition sites in the YAP promoter, the AP-1 transcription factor c-Jun also controls the expression of YAP. When c-Jun is knocked down, YAP is downregulated.[30]

To regulate context-specific gene expression patterns, YAP functions as a transcriptional coactivator by interacting with different transcription factors and epigenetic regulators. YAP interacts with TEAD, β-catenin, FoxO1, and TFEB in embryonic and adult stem cells to control genes related to stemness, differentiation, and stress response.[31] In various cellular situations, the transcriptional outputs and biological roles of YAP are deter-

mined by the particular YAP-interacting partners.

Regulation of YAP by microRNAs:

YAP (Yes-associated protein) is regulated by various microRNAs (miRNAs) through both transcriptional and post-transcriptional mechanisms. Transcriptional regulation of YAP by miR-375 has been studied to repress YAP expression by binding to the YAP mRNA 3'UTR and inhibiting its translation.[32] YAP levels rise when miR-375 is often downregulated in malignancies such as colorectal carcinoma.[33]

Post-transcriptional regulation of YAP by miR-200a-3p has been found to interact with YAP and regulate its function in cervical cancer cells. It has been suggested that miR-200a-3p functions as a negative regulator of YAP because overexpression of the protein can prevent YAP-mediated cell proliferation and metastasis.[34] However, as YAP was also found to offset the effects of miR-200a-3p in some cell lines, the connection between miR-200a-3p and YAP appears to be context-dependent.

Reciprocal Regulation of miRNAs and YAP regulates the expression of specific miRNAs, such as let-7, by modulation of miRNA processing enzyme Dicer. This implies that YAP may also have an indirect impact on miRNA targets' expression, resulting in the formation of an intricate regulatory network.[35]

Epigenetic regulation of YAP:

Epigenetic modifications like histone modification, chromatin remodeling, and DNA methylation play a role in YAP regulation. Inconsistent with its function as a transcriptional coactivator, YAP binding sites are enriched for the enhancer histone mark H3K4me1 and depleted of the promoter mark H3K4me3.[36] YAP appears to occupy active enhancers, as evidenced by the correlation between H3K27ac levels and YAP binding signal levels Lineage-specific YAP binding sites were found close to tissue-specific oncogenes and markers in malignant pleural mesothelioma (MPM).[37]

YAP controls gene expression programs through interactions with chromatin remodeling complexes such as SWI/SNF. It has been discovered that YAP-mediated transcription and carcinogenic activities require the SWI/SNF component ARID1A. The ability of YAP to regulate gene expression and tumor growth is compromised when the YAP-SWI/SNF connection is disrupted.[38]

Considering that the YAP promoter is hypermethylated in specific malignancies like hepatocellular carcinoma, it is evident that DNA methylation can regulate YAP expression.[39] In these circumstances, demethylating drugs can revive YAP expression.

Metabolic regulation of YAP:

YAP activity is regulated by the sterol regulatory element binding protein/mevalonate signaling pathway, an essential cellular metabolic route. YAP/TAZ nuclear localization is inhibited by the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase, according to research by Sorrentino *et al*. Geranylgeranyl pyrophosphate, which is generated by the mevalonate pathway, activates Rho GTPase. This GTPase breaks the bond between angiomotin (AMOT) and YAP by polymerizing F-actin.[40] As a result, YAP can go to the nucleus and start the transcription of pro-growth genes.

Regulation by microenvironment:

The regulation of YAP activity and localization is significantly influenced by the extracellular matrix (ECM) and cytoskeletal tension. Since YAP is primarily cytoplasmic in soft matrix environments, cell growth is inhibited. On the other hand, YAP translocates to the nucleus in a rigid extracellular matrix, encouraging cell division. Cells use the cytoskeleton to detect and react to mechanical stimuli. Nuclear YAP levels rise as a result of F-actin polymerization, which also produces an opposing force to balance tension and promote cell division. ECM rigidity and YAP regulation are linked via the scaffold protein AMOT. AMOT is a YAP inhibitor that works either directly or via kinases LATS1/2 in the Hippo pathway. AMOT binds to F-actin preferentially during F-actin polymerization, removing the inhibitory effect on YAP.[41] Furthermore, F-actin increases nuclear YAP accumulation by inhibiting LATS1/2 activity.

YAP-The key oncogenic pathway of human cancers

Many human malignancies exhibit extensive YAP activation. Nevertheless, most cancers do not initiate because of YAP activation or Hippo kinase inactivation. In the mammalian gut, homeostatic self-renewal and regeneration are generally primarily fueled by the Wnt pathway. Meanwhile, the most frequent cause of colon tumor growth is the constitutive activation of this system.[42] According to research by Seo Y *et al*., cytoplasmic YAP can reduce the formation of intestinal epithelia that regenerates by reducing the activity of Dishevelled,

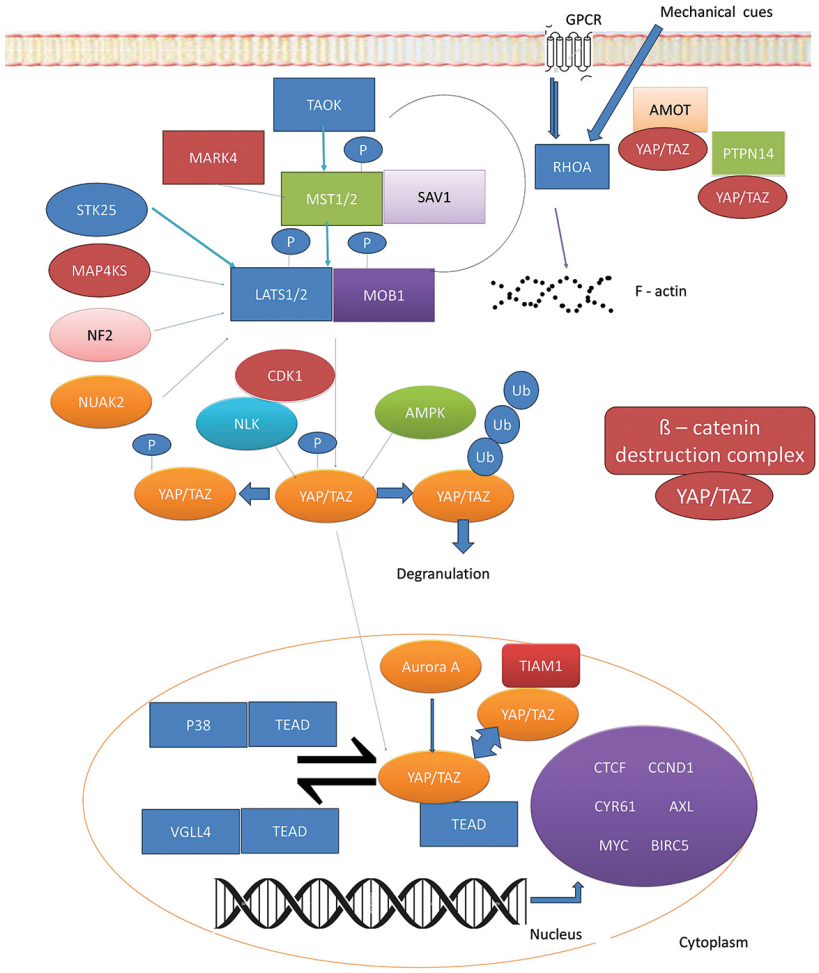

Figure 3: YAP's regulatory mechanism. The classical Hippo pathway, which is composed of MST1/2-SAV1 > LATS1/2-MOB1, is the main regulator of YAP/TAZ. By either ubiquitination and proteasome-mediated destruction or 14-3-3-mediated cytoplasmic sequestration, LATS1/2 phosphorylates YAP/TAZ and renders it inactive. After translocating to the nucleus, unphosphorylated YAP/TAZ interacts with TEAD transcription factors to trigger target genes. TAOK, STK25, MAP4KS, and NF2 activate LATS1/2, whereas F-actin and NUAK2 inactivate it in response to mechanical stimuli and GPCR-mediated RHOA. MARK4 and TAOK activate MST1/2. LATS separately regulates YAP/TAZ as well. YAP/TAZ interacts with AMOT and PTPN14, which sequesters it in the plasma membrane. TIAM1 or the β-catenin destruction complex directly interacts with YAP/TAZ to inhibit it. Additionally, AMPK, CDK1, NLK, Aurora A, and several other proteins directly phosphorylate and control YAP/TAZ.

which in turn limits Wnt signaling.[43] Furthermore, YAP is reactivated to limit the growth of colorectal carcinoma xenografts, and it is silenced in a subpopulation of highly aggressive and undifferentiated human colorectal carcinomas.[44] Thus, via disrupting Wnt signaling, it has been demonstrated that YAP acts as a tumor suppressor in colon cancer. It has also recently been discovered that YAP activation can sustain intestinal epithelial cells in a wound-healing signaling state with decreased Wnt signaling and increased production of Kruppel-like factor 6.[45] On the other hand, colonic tumors that were produced focally grew more quickly when YAP was deleted which is evidence that YAP functioned as a tumor suppressor and that activating hippocampal kinases was a novel therapeutic strategy for the treatment of colorectal cancer.[44]

YAP as a tumor suppressor

Although YAP is involved in carcinogenesis, some research has connected its function to anti-tumor pathways in different kinds of cancer. Low YAP1 expression is associated with poorer prognosis in hematological cancers, and YAP reduces proliferation in multiple myeloma cells via interaction with pro-apoptotic p73.[46]

Breast cancer has been linked to the loss of heterozygosity in chromosome 11q22-q23, which contains YAP1. Additionally, YAP deletion or knockdown in breast cancer

cell lines decreases tumorigenic potential.[47] A recent study demonstrated that, only when YAP is hydroxylated in a prostate cancer cell line, YAP1 knockdown increases the in vitro metastatic potential in cell lines from multiple tissues, indicating a tumor suppressive effect. A subset of neuroendocrine prostate tumors exhibits YAP silencing, suggesting a context-dependent post-translational modification-based tumor suppressive role.[48]

These results imply that, depending on the situation, YAP may display a binary switch between oncogene and tumor suppressor. YAP functions as a tumor suppressor only in certain cases. A tiny group of cancers, including hematological malignancies and small cell neuroendocrine tumors, have YAP silenced as in the majority of the cases it serves as a tumor progressor gene.

Role of YAP in oral cancer

Chronic exposure to risk factors like tobacco and alcohol can lead to genetic alterations in the normal oral mucosa, causing uncontrollable cellular proliferation and rendering cells unable to respond to stress or DNA damage.[49] Modifications to pathways such as p53, p16, cyclin D1, and retinoblastoma protein, lead to oral cancer development. Although there is currently little information linking the Hippo-YAP pathway to the aetiological aspects of oral cancer, it is most likely the case that YAP contributes to metastasis rather than starting the oncogenic process. According to several research, YAP may be an important therapeutic target.[16]

YAP plays a critical role in cell migration by promoting EMT and inhibiting adherens junctions mediated by E-cadherin.[13] Furthermore, in OSCC, YAP is thought to be a biomarker for metastasis and resistance to EGFR inhibitors like cetuximab and gefitinib.[50] With the genetic changes linked to oral cancer, YAP may be a target for therapy even if it may not start the oncogenic process in OSCC but rather drive metastasis.

A lot of research has been done on the carcinogenic function of YAP in a variety of carcinoma types, including OSCC. Research has demonstrated that YAP is considerably overexpressed and amplified in OSCC, suggesting a possible function for it in oncogenesis.[33] In many types of squamous cell carcinomas (SCCs), elevated YAP expression has been associated with nuclear localization, which promotes cell proliferation, invasiveness, and survival.[36] Studies have consistently shown that OSCC tissues exhibit higher levels of YAP than neighboring normal tissues.

YAP in the onset and progression of OSCC

Clinical outcomes and treatment responses in oral cancers can be influenced by the molecular and genetic heterogeneity of the original tumors. This heterogeneity can be better characterized and the disease mechanisms, including metastasis, more thoroughly understood through *in vitro* studies using cancer cell lines. Previous research investigating the Hippo-YAP pathway in OSCC cell lines derived from the buccal mucosa and floor of the mouth demonstrated overexpression of WWTR1 and YAP1, highlighting their potential roles in OSCC pathogenesis.[51]

Recent gene expression profiling of oral squamous cell carcinoma (OSCC) cell lines has identified three major gene signature groups. First, twenty-one genes related to the Hippo pathway-including YAP1, WWTR1, core pathway components, and associated transcription factors-were found to be upregulated in OSCC cell lines. Second, eight genes recognized as cancer biomarkers exhibited higher expression levels in carcinoma cell lines compared to normal oral epithelial cells. Third, seventeen genes involved in intercellular anchoring junctions, such as those encoding desmosomes and adherens junctions, were downregulated in both cancer and dysplastic cells. Notably, the extent of downregulation of these junction-related genes varied among different OSCC cell lines, reflecting the molecular heterogeneity of the disease.[17]

Literature studies on YAP and OSCC

A systematic and comprehensive literature search was conducted to identify relevant studies on the role of Yes-associated protein (YAP) in OSCC and oral precancerous lesions. The search was performed across multiple electronic databases, including PubMed, Scopus, and Web of Science, to ensure broad coverage of biomedical literature published between January 2010 and March 2025. The search terms included "YAP," "Yes-associated protein," "Hippo pathway," "oral squamous cell carcinoma," and "oral cancer." Inclusion criteria were original research and review articles in English focusing on YAP in OSCC or oral precancerous lesions. Exclusion criteria included non-English articles, case reports, and studies

not involving OSCC or YAP

Many authors in the literature have studied the expression of YAP in oral cancer cell lines, mouse models, and human tissues. (Table 1). The authors showed an increased expression of YAP in Oral cancer tissues compared with normal tissues.[52-60] Omron H *et al* reported that the onset of OSCC depends on YAP1 activation, inhibition of which slows the progression of OSCC.[60] Another study done by Ono S *et al*.,[58] showed a positive correlation between increased YAP expression in poorly differentiated OSCC and well-differentiated tissue samples. From this, it is evident that Yap expression can be used as a prognostic marker.

YAP as a therapeutic agent

Yes-associated protein (YAP) has emerged as a prospective target for cancer therapy. Since this complex is necessary for YAP-mediated transcriptional activity and carcinogenic activities, the main focus of YAP cancer therapy has been to break its interaction with TEAD transcription factors.[61]

Numerous small-molecule inhibitors that can attach to YAP and stop it from joining TEAD have been found; these inhibitors limit YAP's capacity to convert in vitro. Vertiporfin (VP), a porphyrin derivative, is one such substance that has been demonstrated to bind to YAP and obstruct the YAP-TEAD interaction. It's interesting to

Table 1: Literature studies on Yap association in OSCC.

S no	Author, Year of study, Country	Hippo component	Methods of Detection	Impact in cancer
1	Li SY, 2013, China.[52]	YAP1	RT PCR; Western blotting; IHC	Increase in cDNA of YAP1 in OSCC tissue; IHC – Increased expression localized in the cytoplasm of OSCC tissue.
2	Hiemer SE *et al*, 2015, The USA.[53]	YAP1	IHCIJC; Immunofluorescence;	Increased nuclear expression of YAP in severe dysplasia High levels of YAP expression in poorly differentiated.
3	Hasegawa K *et al*, 2021, Japan.[54]	YAP1	IHC	Hyperactivated YAP1 expression in OSCC tissues.
4	Ge L, 2011, China.[55]	YAP	IHC	Increased YAP expression in OSCC tissue; Leukoplakia – cytoplasmic expression in basal and parabasal layers; Control – Undetectable; Upregulated expression – Nodal metastasis;
5	Qi L *et al*, 2019, China.[56]	YAP	IHC	Increased expression of YAP than adjacent normal tissue localized in the majority at the nucleus, few in the nucleus, and few in both;
6	Szelachowska J *et al*, 2019, Poland.[57]	YAP	IHC	Expression of YAP with cytoplasmic localization in cancer cells;
7	Ono S *et al*, 2019, Japan.[58]	YAP	IHC	Positive YAP expression in all OSCC tissues; Higher expression in poorly differentiated than well and moderately differentiated; Yap expression increased in poor survival;
8	Zhang L *et al*, 2011, China.[59]	YAP	Western blotting; RTPCR;	High expression of YAP in OSCC cell lines;
9	Omori H *et al*, 2020, Japan.[60]	YAP1	IHC	Increased nuclear YAP 1 expression in OSCC than control; onset of OSCC depends on YAP1 activation; inhibition of YAP1 slows the progression of OSCC.

note that VP has clinical approval for the treatment of macular degeneration. In preclinical research, VP was repeatedly administered in a mouse model of liver cancer to effectively decrease hepatic expansion and delay tumor progression without having a major negative impact on other organs.[62]

YAP can be directly targeted, but it can also be activated by blocking the Hippo pathway's upstream kinases, like Mst1 and Mst2. For instance, it has been demonstrated that the Mst1 inhibitor 9E1 increases YAP function. Additionally, it has been discovered that dasatinib, a Src family kinase inhibitor, inhibits the kinase YES1, which inactivates the YAP1-β-catenin-TBX5 complex and reduces the proliferation of cells that are active with β-catenin.[63]

Targeting the YAP-TEAD connection, whether directly or indirectly, has shown promising results in preclinical research and warrants further investigation as a potential therapeutic approach for cancer.

Conclusions

Although YAP overexpression has been reported in various cancers, including oral squamous cell carcinoma (OSCC), its precise role in disease progression and prognosis remains uncertain. Importantly, YAP abundance alone-particularly given its predominantly nuclear localization-may not accurately reflect its functional activity, as treatment resistance in OSCC cells is influenced by the complex interplay between YAP, TAZ, and the broader Hippo-YAP pathway. While there is increasing interest in YAP's involvement in the neoplastic process and its potential as a therapeutic target, current evidence specifically linking YAP to the onset and progression of OSCC is limited, and strong conclusions regarding its prognostic value are not yet warranted. Many aspects of Hippo pathway signaling in OSCC, including its influence on cell junction adhesion, structural integrity, invasion, and metastasis, remain to be fully elucidated. Therefore, further *in vivo* validation and comprehensive clinical studies are needed to clarify the diverse functions of YAP in OSCC, and future research in these areas will be essential for advancing our understanding of the disease and evaluating the potential of YAP as a biomarker or therapeutic target.

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