DECODING YAP-DRIVEN MALIGNANT REPROGRAMMING IN ORAL EPITHELIAL STEM CELLS THROUGH SINGLE-CELL ANALYSIS

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ABSTRACT

Oral squamous cell carcinoma (OSCC), a major subtype of head and neck squamous cell carcinoma (HNSC), is characterized by high mortality rates and cellular heterogeneity that complicates early detection and treatment. Recent advances in cancer biology suggest that tumorigenesis involves reprogramming of epithelial progenitor cells into cancer stem-like cells (CSCs), driven by oncogenic signaling such as Yes-associated protein (YAP) activation. YAP, a key effector of the Hippo pathway, regulates transcriptional programs involved in cell proliferation, dedifferentiation, and inhibition of differentiation. However, the specific mechanisms by which YAP reprograms oral epithelial stem cells remain incompletely understood. This literature review systematically explores findings from studies published between 2020 and 2025 that investigate the role of YAP in malignant reprogramming, particularly through single-cell analysis approaches. Articles were sourced from PubMed and Google Scholar using defined inclusion criteria, focusing on original studies involving in vitro, in vivo, or bioinformatic models. The review highlights that YAP activation in oral epithelial cells induces stemness-associated genes (e.g., SOX2, NANOG, OCT4), represses differentiation pathways (Notch, p63), and promotes epithelial-mesenchymal transition (EMT) markers (ZEB1, SNAI2, VIM). Single-cell RNA sequencing (scRNA-seq) has revealed dynamic and hybrid cell states, supporting the view that YAP-driven transformation is gradual and reversible. YAP also shapes the tumor microenvironment by inducing cytokines that recruit tumor-supportive immune and stromal cells. Key YAP-regulated targets such as CTGF, AXL, and ITGA6 emerge as potential therapeutic entry points, as their inhibition reduces proliferation and stemness. These findings underscore YAP's central role in oral carcinogenesis and its promise as a molecular target for early intervention and therapy.

Keywords : YAP, oral epithelial stem cells, malignant reprogramming, cancer stem cells

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is one of the most common forms of head and neck cancer, characterized by high morbidity and mortality rates. The latest model of how cancer develops suggests that the formation of a tumor requires two simultaneous processes: first, the activation of genes that promote cancer growth (oncogenes); and second, the failure of the body's natural mechanisms that normally prevent tumor growth—such as normal cell maturation, stress-induced premature aging, and programmed cell death. This understanding is supported by recent studies that use genome sequencing

technology to map various genetic changes believed to be key drivers of cancer in humans. However, most of these studies have been conducted on tumors that are already advanced and composed of diverse cell types with numerous genetic mutations. This makes it difficult for researchers to identify which cells initially triggered the cancer and to distinguish between genetic changes that cause cancer and those that merely worsen it. As a result, the molecular mechanisms that explain how immature normal cells transform into cancer-initiating cells remain not fully understood (Campbell et al., 2020; Cao et al., 2022; Saikia et al., 2023; Chakravarty et al., 2024; Cabral et al., 2025).

Head and neck squamous cell carcinoma (HNSC) is a type of cancer that most commonly originates from the epithelium of the upper respiratory and digestive tracts. Large-scale molecular analyses of HNSC have shown that, despite the wide range of genetic mutations across tumors, most of these changes converge on a limited number of oncogenic molecular pathways. HNSC is characteristically marked by inactivation of the tumor suppressor genes TP53 and CDKN2A, either through direct mutation or inhibition by the viral proteins E6 and E7 produced by human papillomavirus (HPV). Previous studies have reported that mutations in the FAT1 gene, found in approximately one-third of HNSC cases, disrupt regulation of the Hippo pathway, subsequently leading to uncontrolled activation of the transcriptional co-activator YAP. In addition to FAT1 mutations, several other genomic alterations identified in HNSC have also been associated with disruption of the Hippo pathway and activation of YAP. Nevertheless, the direct impact of excessive YAP activation on the tumor initiation process remains not fully understood (Faraji et al., 2025; Khan et al., 2025; Shanmugam et al., 2025).

Yes-associated protein (YAP) is a key transcriptional co-activator in the Hippo signaling pathway, playing a crucial role in regulating cell proliferation, apoptosis, and tissue homeostasis. YAP activation has been linked to the development of various types of cancer, including OSCC. Studies have shown that the accumulation of YAP in the nucleus can promote cell proliferation and inhibit differentiation, contributing to the malignant transformation of oral epithelial cells (Dong et al., 2019).

YAP activation, especially in combination with other oncogenes such as HPV E6/E7, can reprogram oral epithelial progenitor cells into cancer stem cells (CSCs). This process is marked by the activation of oncogenic transcriptional programs, mTOR signaling, and the recruitment of myeloid cells to invasive areas, all of which contribute to tumor infiltration (Faraji et al., 2025).

Single-cell analysis technology has revolutionized our understanding of cellular heterogeneity within tumors. With single-cell resolution, this approach enables the identification of specific cell subpopulations, including CSCs, and the transcriptional pathways active during tumor initiation. In the context of OSCC, single-cell analysis has revealed that the transcriptional programs triggered by YAP in the early stages of tumorigenesis mirror those found in human head and neck cancers and are associated with poor patient prognosis (Song et al., 2022; Wang et al., 2024; Liu et al., 2025).

The identity of the cell of origin for HNSC and the early mechanisms involved in its initiation are still not fully understood. In the oral epithelium, there are oral epithelial progenitor cells (OEPCs) located in the basal layer of the stratified squamous epithelium. These cells have the ability to self-renew continuously and differentiate into various cell types that form the epithelial structures of the tongue and soft palate. Given their central role in tissue regeneration and maintenance, OEPCs are considered strong candidates for being the cell of origin of HNSC. Therefore, the oral epithelium provides a relevant model system for studying the early molecular events

underlying the malignant transformation of normal cells into cancer cells (Byrd et al., 2019; Faraji et al., 2024; Seubert et al., 2024; Faraji et al., 2025).

This study aims to elucidate the malignant reprogramming mechanisms mediated by YAP in oral epithelial stem cells using a single-cell analysis approach. By understanding the transcriptional pathways and phenotypic changes that occur during this transformation, the study hopes to identify potential targets for early detection and prevention of oral cancer.

MATERIALS AND METHODS

This study was conducted using a literature review approach aimed at summarizing and analyzing recent findings on the role of YAP (Yes-associated protein) in the malignant reprogramming of oral epithelial stem cells, particularly through single-cell analysis. Literature was systematically searched using electronic databases PubMed and Google Scholar with main keywords such as “YAP,” “oral epithelial stem cells,” “malignant reprogramming,” and “single-cell analysis.” Selected articles were English-language publications from the period 2020 to 2025. Inclusion criteria encompassed original research articles involving in vitro, in vivo, or bioinformatics studies that highlighted the relationship between YAP activity and phenotypic or transcriptomic changes in oral epithelial stem cells. Review articles, commentaries, and case reports were excluded from the analysis. Literature that met the criteria was manually selected based on content relevance and methodological quality. Data from each study were narratively analyzed to identify patterns, research gaps, and recent conceptual developments in understanding YAP-driven malignant reprogramming mechanisms.

The literature screening process was carried out in stages to ensure that only relevant and high-quality articles were analyzed in this study. The initial stage involved selecting articles based on their titles and abstracts to identify studies that explicitly discussed the role of YAP in malignant reprogramming of oral epithelial stem cells using a single-cell analysis approach. Articles not directly relevant to the topic were eliminated. The next phase involved a full-text review of articles that passed the initial screening. Articles retained were original research studies conducted on appropriate biological models—such as human or animal oral epithelial stem cells—and employed single-cell RNA sequencing or other relevant single-cell analysis methods. Studies that discussed YAP only in general terms, did not focus on oral epithelial stem cells, or did not provide primary data were excluded. Articles that were not available in full text, not published in English, or published before 2020 were also excluded. To maintain data uniqueness, checks were also performed for duplicate or redundant publications from the same research groups to avoid redundancy in interpretation.

RESULT AND DISCUSSION

Research over the past few years has shown that activation of YAP (Yes-associated protein) plays a crucial role in the transition of normal oral epithelial cells into a cancer phenotype resembling cancer stem-like cells. This mechanism involves broad regulation of gene expression that triggers proliferation, dedifferentiation, and resistance to terminal differentiation (Faraji et al., 2023).

Several recent studies have shown that abnormal activation of YAP (Yes-associated protein), as part of the Hippo pathway, significantly contributes to malignant transformation in various epithelial tissues, including oral epithelium. YAP is known to function as a transcriptional co-activator that translocates to the cell nucleus when the Hippo pathway is inactivated, thereby inducing the expression of genes that promote proliferation, inhibition of differentiation, and stemness (Deng et al., 2021; Amano et al., 2024).

In oral epithelial tissue, YAP is abnormally activated in precancerous and cancerous conditions and is associated with increased expression of stemness-related genes such as SOX2, NANOG, and OCT4. This activation causes basal cells to lose the normal epithelial differentiation program and undergo dedifferentiation toward a malignant stem cell state. scRNA-seq studies have reported the emergence of cell populations with high expression of TEAD target genes, including CTGF and CYR61, which play roles in pro-tumor signal transduction (Roy et al., 2024; Faraji et al., 2025).

YAP promotes cellular plasticity, which is the ability of cells to shift between different differentiation states. In a mouse model with YAP overexpression in oral tissue, scRNA-seq analysis revealed a phenotypic transition from basal cells toward a mesenchymal phenotype, accompanied by increased expression of EMT markers such as ZEB1, SNAI2, and VIM (Liu et al., 2021; Shang et al., 2023). This plasticity contributes to enhanced migration, invasion, and therapy resistance.

In addition to its intrinsic effects, YAP plays a role in shaping the tumor microenvironment (TME). Several studies have shown that YAP activation in oral epithelial cells influences the expression of cytokines such as IL-6, TGF-β, and CXCL12, which attract macrophages and fibroblasts to create a TME that supports tumorigenesis. This environment helps maintain cancer stem cells within a niche that supports their self-renewal (Ortega et al., 2021; Xu et al., 2023; Athavale et al., 2024).

Several studies have shown that YAP activation inhibits the Notch and p63 pathways, which normally mediate oral epithelial differentiation. The suppression of KRT4, KRT13, and IVL expression indicates that YAP maintains cells in an undifferentiated state, prolonging their lifespan and increasing their potential for malignant transformation (Ning et al., 2023; Pankratova et al., 2024).

Single-cell transcriptomics approaches reveal heterogeneity that is not detectable through bulk analysis. Several cell clusters exhibit mixed expression of basal, mesenchymal, and stem-like markers, indicating the presence of dynamic transitions and hybrid cell identities. These findings support the hypothesis that YAP-driven reprogramming is not a binary event, but rather a gradual and reversible process (Thong et al., 2020; Caruso et al., 2024).

The identification of YAP-regulated targets, such as AXL, ITGA6, and CD44, opens up possibilities for pharmacological intervention. Knockdown studies using siRNA or specific inhibitors have shown that inhibition of the YAP/TEAD pathway can reduce proliferative capacity and limit the colony-forming ability of oral cancer cells. Therefore, YAP is not only an important biomarker but also a strategic therapeutic target in stem cell–based oral cancer treatment (Ahmad et al., 2022; Faraji et al., 2025).

The results of the literature review indicate that activation of Yes-associated protein (YAP) plays a central role in driving malignant reprogramming in oral epithelial stem cells. YAP functions as a key transcriptional regulator within the Hippo pathway and, when abnormally activated, promotes the expression of pro-tumorigenic genes that support cell proliferation, plasticity,

and the inhibition of differentiation (Ahmad et al., 2022; Faraji et al., 2025).

One of the major findings across multiple studies is that YAP shifts the identity of basal oral epithelial cells toward a cancer stem cell–like state, marked by increased expression of SOX2, NANOG, OCT4, and proliferative markers such as MKI67. This transition reflects a dedifferentiation process, in which normal epithelial cells revert to a more primitive and plastic state—characteristics typical of cancer stem cells. This aligns with contemporary cancer biology models that emphasize the role of "cancer stem-like" populations in tumor initiation, progression, and therapeutic resistance (Fu et al., 2016; Naini et al., 2019).

The application of single-cell RNA sequencing (scRNA-seq) has significantly contributed to uncovering intratumoral heterogeneity and the cellular transition trajectories induced by YAP activation. Unlike bulk RNA analysis, which masks cell-to-cell variability, scRNA-seq enables the identification of distinct cell clusters exhibiting mixed characteristics of basal epithelial, stem-like, and mesenchymal states. These hybrid identities illustrate the biological reality that YAP-induced transformation is not a linear event but a dynamic adaptation shaped by the tumor microenvironment and additional transcriptional regulators (Lai et al., 2021; Zhan et al., 2025; Yan et al., 2025).

Furthermore, YAP-induced reprogramming is not purely intrinsic; it also involves modulation of the tumor microenvironment (TME). YAP activation is associated with increased secretion of pro-inflammatory cytokines and chemotactic factors, which recruit macrophages, fibroblasts, and other immune cells to create a tumorigenic niche. The interaction between reprogrammed epithelial cells and the TME reinforces the survival and self-renewal of oral cancer stem cells (Faraji et al., 2024).

Another key observation is that YAP does not act alone—it collaborates with cofactors such as TEAD1/4 and suppresses differentiation pathways including Notch and p63. The downregulation of epithelial differentiation markers such as KRT4 and IVL indicates that YAP actively maintains an undifferentiated state. In essence, YAP creates a cellular condition in which cells are "locked" in a plastic state—avoiding terminal differentiation while retaining high transformational potential (Totaro et al., 2017; Gokey et al., 2021; Ning et al., 2023).

The clinical implications of these insights are substantial. The identification of YAP downstream target genes such as CTGF, AXL, and ITGA6 opens new avenues for more precise molecular therapies. Knockdown studies have shown that inhibiting these targets can reduce the proliferative capacity and colony-forming ability of reprogrammed cells. This suggests that YAP and its regulatory network represent valid and promising therapeutic targets for oral cancer treatment strategies focused on controlling stemness and plasticity (Tang et al., 2023).

Nevertheless, several research gaps remain to be addressed. Most current studies are based on animal models or in vitro systems, with limited clinical validation in oral cancer patients. Additionally, the temporal dynamics of YAP activation during tumor progression are still not fully understood. Whether YAP activation is an initiating event or a secondary response in oral epithelial carcinogenesis remains an open question. There is also the possibility of redundancy or compensation by other signaling pathways—such as Wnt or TGF-β—that may either counteract or enhance YAP's effects (Park et al., 2015; Faraji et al., 2025).

Further bioinformatic analysis identified several potential target genes regulated by YAP that play a critical role in maintaining the malignant stem-like state, including CTGF, AXL, and ITGA6.

Knockdown experiments using siRNA against these targets showed a reduction in the proliferation and self-renewal capacity of reprogrammed epithelial cells, indicating the therapeutic potential of inhibiting this pathway. This understanding not only expands insights into cancer stem cell biology but also opens opportunities for developing therapies that target YAP or related transcriptional pathways as a strategic approach to inhibit cellular transformation in oral cancer (Ghiso et al., 2017; Kim et al., 2021).

SUMMARY

Abnormal activation of Yes-associated protein (YAP) plays a key role in transforming normal oral epithelial cells into cancer stem cell–like cells. YAP activates genes that promote proliferation, dedifferentiation, and cellular plasticity, while suppressing differentiation pathways such as Notch and p63.

scRNA-seq analysis has revealed that YAP activation gives rise to cells with mixed identities—basal, stem-like, and mesenchymal—indicating that this transformation is dynamic in nature. YAP also influences the tumor microenvironment (TME) by inducing cytokines that recruit tumor-supporting cells, thereby reinforcing stem-like properties.

YAP targets such as CTGF, AXL, and ITGA6 have been shown to be essential for cancer cell survival, and their inhibition reduces proliferation and colony-forming ability. These findings highlight the central role of YAP in malignant reprogramming and present opportunities for molecular therapies in oral cancer.

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