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Hypoxia Inducible Factor-2α in Oral Biology Research: A Narrative Review

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Abstract

Hypoxia, characterized by low oxygen tension, is frequently observed in various stressed tissues, including tumors, wounds, and inflammatory lesions. Hypoxia-inducible factors (HIFs), such as HIF-1α and HIF-2α, heterodimerize with a beta subunit (ARNT) to initiate the transcription of various genes, including VEGF, erythropoietin, and glycolytic enzymes, which are essential for cellular survival, adaptation, and angiogenesis promotion. HIF-2α exhibits both overlapping and unique functions in comparison to HIF-1α, influenced by cell type, oxygen levels (moderate versus severe hypoxia), and contextual factors (chronic versus acute hypoxia). On PubMed and Google Scholar, the scholarly literature on the subject of Hypoxia inducible factor 2α in Oral Biology research was analyzed. Articles that discussed or looked into the effects of Hypoxia inducible factor 2α in Oral biology on dentistry were looked for in search results. The cited papers from the journals were also evaluated for relevance and included if they met the requirements for inclusion. One of the requirements for admittance was having access to the entire material.

Conclusion: HIF-2α is definitely expressed in oral SCC and premalignant oral lesions, correlates with tumor features like stage, angiogenesis. Functionally, HIF-2α contributes to OSCC progression, especially via angiogenesis, and may be more predictive in certain hypoxia conditions. But in oral biology outside of cancer, and in temporal and mechanistic depth, HIF-2α remains under-explored.

Keywords: HIF-1α ; HIF-2α; VEGF; Wound Healing; OSCC

1. Introduction

Hypoxia, characterized by low oxygen tension, is frequently observed in various stressed tissues, including tumors, wounds, and inflammatory lesions. Cells utilize the hypoxia-inducible factor (HIF) family of transcription factors for adaptation. Hypoxia-inducible factors (HIFs), such as HIF-1α and HIF-2α, heterodimerize with a beta subunit (ARNT) to initiate the transcription of various genes, including VEGF, erythropoietin, and glycolytic enzymes, which are essential for cellular survival, adaptation, and angiogenesis promotion. HIF-2α exhibits both overlapping and unique functions in comparison to HIF-1α, influenced by cell type, oxygen levels (moderate versus severe hypoxia), and contextual factors (chronic versus acute hypoxia). In the field of oral biology, encompassing oral squamous cell carcinoma (OSCC), oral potentially malignant disorders, wound healing (both mucosal and bone), and inflammation, the significance of hypoxia and HIF-mediated responses is gaining recognition. In contrast to HIF-1α, HIF-2α has been less extensively researched in the oral cavity. This narrative examines the current understanding of HIF-2α in oral biology, including evidence, functional roles, existing gaps, and therapeutic implications.1-5

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2. Methods

On PubMed and Google Scholar, the scholarly literature on the subject of Hypoxia inducible factor 2α in Oral Biology research was analyzed. Articles that discussed or looked into the effects of Hypoxia inducible factor 2α in Oral biology on dentistry were looked for in search results. The cited papers from the journals were also evaluated for relevance and included if they met the requirements for inclusion. One of the requirements for admittance was having access to the entire material (Table 1).

Table 1 Research Method and Criteria for Choosing Studies

	Research Method and Criteria for Choosing Studies
A	The literature on Hypoxia inducible factor 2α in Oral Biology studies was explored through PubMed and Google Scholar. Techniques for searching were utilized through the combinations. "Name of Hypoxia inducible factor 2α" + "Oral Biology" in relation to the terms "HIF2α", "oral cancer", "bone regeneration", and "Mucosal regeneration". The papers were assessed based on the inclusion criteria from January 1, 2000, to August 31, 2025, and were written in English.
B	- Language: English; Publication period: January 1, 2000 – August 31, 2025; The publications included reviews, book chapters, original research papers, in vitro investigations, in vivo studies involving animals or humans, clinical trials, and meta-analyses. - Case studies, letters, editorials, studies with unnecessary or irrelevant data, incomplete pieces, and articles not written in English were all excluded.

2.1. Expression of HIF-2α in Oral Lesions and OSCC

- Numerous studies have investigated the immunohistochemical expression of HIF-2α in oral potentially malignant disorders, such as oral submucous fibrosis (OSF) and oral squamous cell carcinoma (OSCC), and have frequently compared it with HIF-1α to assess correlations with histological grade, stage, and differentiation. 6-8
- A study examined HIF-2α immunohistochemistry in patients with oral submucous fibrosis (OSF), oral squamous cell carcinoma (OSCC) (with and without areca nut usage), and normal oral mucosa. Elevated levels of HIF-2α are reported in OSCC relative to normal mucosa. Lippincott Journals.6
- Enhanced specificity: Hypoxia inducible factor-1α and hypoxia inducible factor-2α exhibit distinct yet functionally overlapping roles in oral squamous cell carcinoma, as evidenced by a study involving 97 OSCC patients that explores clinical-pathological correlations. HIF-2α expression was associated with T stage and micro vessel density, but showed a weaker correlation with lymph node involvement or histologic differentiation than HIF-1α. PubMed is a comprehensive database of biomedical literature, providing access to a vast array of research articles and clinical studies. 7
- A recent study titled ("Hypoxia inducible factor-2 expression in OSF, OSCC"), which examined 90 cases of OSCC, found that all cases exhibited some level of positivity for both HIF-1α and HIF-2α. The study indicated that the mean labeling index (MLI) for HIF-2α exceeded that of HIF-1α in both well and poorly differentiated OSCC. Furthermore, HIF-2α localization was predominantly cytoplasmic in well-differentiated tumors, whereas it was nuclear in poorly differentiated tumors. The authors proposed that HIF-2α could serve as a more sensitive and specific surrogate marker for hypoxia in OSCC. PubMed Plus One
- In a recent study (2025), the interaction between hypoxia-inducible factors in the pathology of oral squamous cell carcinoma was investigated. The research revealed significantly higher expressions of both HIF-1α and HIF-2α in OSCC compared to normal oral mucosa, with HIF-2α levels being elevated and correlating with the cancer-associated fibroblast marker α-SMA. The correlations with histologic grade were less pronounced.8
- WAOCP Journal In summary, HIF-2α is expressed in oral cancer and tends to be more detectable in advanced disease stages. It correlates with characteristics such as tumor size and T stage, as well as angiogenesis, indicated by micro vessel density. Additionally, it exhibits nuclear localization in more aggressive or poorly differentiated tumors.9

2.2. Biological Functions

HIF-2α is an oxygen-regulated transcription factor that dimerizes with ARNT, recruits coactivators such as p300, and binds hypoxia response elements to induce genes controlling angiogenesis, metabolism, proliferation, and survival. This core mechanism and target set (for example VEGFA, CCND1, CXCR4, SLC2A1) are summarized in recent overviews of HIF-2α biology and modulators. HIF-2α stability and activity are controlled at multiple levels including

oxygen-dependent prolyl hydroxylases, VHL-mediated ubiquitination, promoter and post-transcriptional regulation, and many post-translational modifications identified in integrative OMICs maps of EPAS1 regulation. Core mechanism HIF-2α forms a PAS-domain heterodimer with HIF-β (ARNT) and activates transcription via HREs and p300 recruitment Oxygen sensing Prolyl hydroxylation targets HIF-α subunits to VHL for degradation; hypoxia blocks this, allowing accumulation. Transcript stability and noncoding regulation EPAS1/HIF-2α shows resistance and complex regulation by miRNAs and RNA-binding mechanisms that prolong expression during hypoxia. Activation kinetics HIF-2α often accumulates under mild or chronic hypoxia and can thus regulate a partly distinct transcriptional program from HIF-1α.10-13

2.3. Functional Studies: The Role of HIF-2α Compared to HIF-1α in Oral Cancer

Several studies have aimed to differentiate the functional roles of HIF-1α and HIF-2α in OSCC. The research involving 97 OSCC patients employed the knockdown of HIF-1α or HIF-2α using shRNA in both cell lines and xenograft models.14-15

Under moderate hypoxia (5% O_2), HIF-2α was the primary contributor to VEGF expression; in contrast, under more severe hypoxia (1%), both HIF-1α and HIF-2α were involved in the regulation of VEGF. Genes such as GLUT1, CA9, and uPAR were predominantly regulated by HIF-1α. PubMed is a comprehensive database that provides access to a vast collection of biomedical literature, including research articles, reviews, and clinical studies. It serves as a critical resource for researchers, healthcare professionals, and students in the field of medicine and life sciences. Knockdown of either HIF-1α or HIF-2α resulted in the inhibition of OSCC cell tumor growth and angiogenesis; dual knockdown exhibited more pronounced effects. PubMed is a comprehensive database of biomedical literature, providing access to a vast array of research articles and clinical studies. HIF-2α is functionally significant, contributing to angiogenesis and tumor growth, and mediating the response to moderate levels of hypoxia, with some overlap yet partial distinction from HIF-1α.

2.4. Wound Healing, Inflammation, and Other Oral Biology Aspects

There is limited knowledge regarding HIF-2α in non-cancerous oral biology, including wound healing (mucosal or alveolar) and periodontal disease. Indirect evidence is present. In a study examining severe intermittent hypoxia, a downregulation of HIF-2α was noted, accompanied by impaired wound healing and a shift in macrophage phenotype towards a pro-inflammatory (M1) state rather than an anti-inflammatory (M2) state. This indicates that HIF-2α facilitates anti-inflammatory and healing processes. HIF-2α has been examined extensively in the context of skeletal repair and osteogenesis, particularly in relation to bone biology, though often not specifically in oral alveolar bone. A review indicates that HIF-2α is involved in the functions of osteoblasts and osteoclasts, potentially contributing to age-related bone loss. Additionally, it is regulated by NF-κB in certain contexts, and there is evidence of cross-regulation between HIF-1α and HIF-2α in specific experimental systems. Specific studies examining HIF-2α in oral wound healing, such as post-tooth extraction sockets and oral mucosal healing, are limited or lacking in the current literature, based on recent findings. Most studies on wound healing and regeneration in the oral cavity predominantly focus on HIF-1α.16-18

3. Comparative Behavior: HIF-1α vs HIF-2α in Oral Biology

3.1. From the studies, several comparative observations emerge

Table 1 Comparative observation between HIF-1α and HIF-2α

Feature	HIF-1α	HIF-2α
Responsiveness to acute, severe hypoxia	More rapidly induced; major early actor	Sustained, especially under moderate or chronic hypoxia; more stable over time
Pattern of target genes	Regulates many hypoxia-responsive genes such as GLUT1, CA9, upper, etc., in many settings	Also contributes to angiogenic genes like VEGF, especially under certain oxygen tensions; may regulate some genes distinct from HIF-1α
Prognostic/predictive value in OSCC	Expression generally correlates with worse outcomes (advanced stage, lymph node metastasis, etc.)	Also correlated, though sometimes weaker; in some studies, HIF-2α shows higher labeling

		in OSCC and better discrimination under certain conditions
Localization (subcellular)	Nuclear/cytoplasmic; nuclear localization tends to indicate activation	Similar; nuclear localization in more aggressive / poorly differentiated tumors; cytoplasmic in less aggressive ones
Therapeutic target potential	Many studies and some preclinical work; more is known	Less well explored; but some studies suggest that dual targeting of HIF-1α + HIF-2α has more effect than targeting either alone in OSCC xenografts.

3.2. Gaps, Uncertainties, and Challenges

While progress has been made, there are many gaps in knowledge about HIF-2α in oral biology

- **Limited studies in non-cancer oral tissues**: wound healing (mucosa, alveolar bone), periodontal disease, inflammatory lesions, etc., have few data specifically for HIF-2α.
- **Mechanistic details**: exactly which downstream genes are uniquely regulated by HIF-2α vs HIF-1α in different oral cell types (keratinocytes, fibroblasts, endothelial cells, osteoblasts etc.) are not fully mapped.
- **Temporal dynamics**: how HIF-2α behaves over time during hypoxia, reoxygenation, intermittent hypoxia in oral tissues is understudied.
- **Clinical prognostic utility**: whether measuring HIF-2α expression (e.g. IHC or molecular) adds independent predictive/prognostic power beyond standard markers (TNM, grading, etc.) in OSCC is promising but not yet fully validated in large cohorts.
- **Therapeutic targeting**: There is less work on inhibitors or modulators of HIF-2α in the oral context—most drug trials target hypoxia or HIF broadly, but not specific HIF-2α inhibitors in OSCC or other oral pathologies.
- **Interaction with microenvironment**: e.g., cancer-associated fibroblasts (CAFs), immune cells, macrophage polarization, extracellular matrix etc.—the cross-talk mediated by HIF-2α in oral tumors or lesions is less well defined.
- **Subcellular and post-translational regulation**: nuclear translocation, stabilization, degradation pathways specific to HIF-2α in oral tissues are not well delineated.

3.3. Therapeutic and Translational Implications

Based on what is known, some directions appear promising:19-20

- **Diagnostic / Prognostic Biomarker**: HIF-2α could be used in IHC panels, possibly in combination with HIF-1α, VEGF, CA9 etc., to stratify OSCC patients in terms of aggressiveness, expected angiogenesis, etc.
- **Combined Targeting**: Since some studies show that dual knockdown of HIF-1α and HIF-2α gives greater suppression of tumor growth and angiogenesis than either alone, therapies that inhibit both, or combined therapies, might be more effective.
- **Exploiting moderate hypoxia**: Because HIF-2α seems especially active under moderate or chronic hypoxia (vs severe), interventions that influence oxygen levels (hyperbaric oxygen, oxygen delivery, etc.) might modulate HIF-2α activity.
- **Regulators of HIF-2α**: Understanding its upstream regulators (e.g. oxygen sensors, prolyl hydroxylases, signaling pathways, maybe inflammatory signals) might allow modulation without directly targeting HIF-2α.
- **Wound healing enhancement**: If HIF-2α supports anti-inflammatory macrophage polarization, angiogenesis, tissue repair, there might be potential in harnessing HIF-2α (or avoiding its down-regulation) in oral wound settings (socket healing, mucosal repair, etc.).
- **Therapeutic inhibitors**: In other fields, HIF-2α inhibitors (e.g. PT2385 in glioblastoma) are being explored. Whether those or similar agents could be useful in OSCC or pre-malignant oral lesions is an open question.

3.4. A Conceptual Model

3.4.1. HIF-2α's role in oral biology

- Early in lesion formation, or under moderate hypoxia (for example in OSF or dysplastic lesions), HIF-2α may become stabilized, promoting VEGF, mild angiogenesis, helping cells adapt.

- As lesions progress to more aggressive forms, HIF-1α may dominate under more severe hypoxia, with more widespread induction of metabolic reprogramming, etc., but HIF-2α still contributes, especially for long-term or chronic effects.
- There may be a "division of labor": HIF-1α is faster, more responsive to acute severe hypoxia, controlling genes needed for immediate survival; HIF-2α is slower but more sustained, contributes to long-term adaptations, angiogenesis, possibly stemness, perhaps chemo-resistance or invasiveness.
- The microenvironment (CAF, immune cells, extracellular matrix stiffness etc.) modulates HIF-2α expression, possibly via cross signalling (inflammatory cytokines, reactive oxygen species, etc.).

4. Conclusion

- HIF-2α is definitely expressed in OSCC and premalignant oral lesions, correlates with tumor features like stage, angiogenesis, etc.

- Functionally, HIF-2α contributes to OSCC progression, especially via angiogenesis, and may be more predictive in certain hypoxia conditions. But in oral biology outside of cancer, and in temporal and mechanistic depth, HIF-2α remains under-explored.

4.1. For future research, priorities might include

- **Larger cohort studies** of OSCC, including longitudinal follow-up, to validate HIF-2α as prognostic / predictive biomarker.
- **In vitro and in vivo mechanistic studies** in oral cell types beyond cancer: keratinocytes, oral fibroblasts, osteoblasts, etc., to map HIF-2α targets.
- **Oral wound healing models** that test the impact of modulating HIF-2α (e.g. via stabilizers or inhibitors) on healing, angiogenesis, inflammation.
- **Interplay with immune cells and CAFs**: how HIF-2α influences or is influenced by macrophage polarization, fibroblasts, ECM remodeling in oral tumors or healing tissue.
- **Therapeutic development**: testing HIF-2α inhibitors (or dual HIF inhibitors) in preclinical OSCC models; exploring small molecules, siRNA/shRNA, or newer modalities.
- **Temporal dynamics**: how intermittent vs continuous hypoxia affects HIF-2α, and whether hypoxia modulation therapies have impact.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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