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Comprehensive insights into the understanding of hypoxia in ameloblastoma

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Summary. Hypoxia is characterized by a disparity between supply and demand of oxygen. The association between hypoxia and head and neck tumors is a topic of significant interest. Tumors frequently encounter areas with inadequate oxygen supply, resulting in a hypoxic microenvironment.

Ameloblastoma is one of the most common benign odontogenic tumors of the maxillofacial region. It is a slow-growing but locally invasive tumor with a high recurrence rate. The literature has demonstrated the correlation between hypoxia and ameloblastoma, revealing a discernible link between the heightened expression of hypoxic markers in low oxygen conditions. This association is intricately tied to the tumoral potential for invasion, progression, and malignant transformation.

Hypoxia profoundly influences the molecular and cellular landscape within ameloblastic lesions. The present review sheds light on the mechanisms, implications, and emerging perspectives in understanding this intriguing association to clarify the dynamic relationship between hypoxia and ameloblastoma.

Key words: Ameloblastoma, Hypoxia, HIF-1α, Odontogenic tumors

Introduction

Hypoxia is characterized by a disparity between the supply of oxygen (O_2) and the demand for O_2 (Samaja and Ottolenghi, 2023). Early observations regarding the impact of reduced O_2 levels date back to the late 18th century when scientists began to recognize the effects of altitude on human physiology (Neville, 1974; Hancock, 2022). In the 19th century, Dr Paul Bert's research on the impact of reduced atmospheric pressure and oxygen at high altitudes laid the foundation for understanding physiological responses to hypoxia (West and Richalet, 2013; West, 2016). In the subsequent years, new discoveries continued to unfold (Samaja and Ottolenghi, 2023). In the medical domain, hypoxia became a key factor in various pathological conditions (Chen et al., 2020).

The intricate interplay between hypoxia and ameloblastoma unveils a captivating facet in oral pathology. Hypoxia profoundly influences the molecular and cellular landscape within ameloblastic lesions. The present review sheds light on the mechanisms, implications, and emerging perspectives in understanding this intriguing association to clarify the dynamic relationship between hypoxia and ameloblastoma.

Hypoxia signaling pathways

Molecular O_2 is indispensable for mammalian cell functioning. It is consumed in various biochemical reactions, including adenosine 5'-triphosphate (ATP) synthesis. To cope with reduced O_2 concentrations, mammalian cells need to adapt, *e.g.*, by reducing ATP-consuming reactions, altering cellular metabolism, or increasing angiogenesis, to ensure an oxygen balance that supports essential cellular activities until appropriate oxygen levels are restored (Luo et al., 2022). Cellular hypoxia is when O_2 levels are between 0.5-2%, and O_2 depletion (anoxia) when O_2 levels are below 0.5% (Lee et al., 2020).

Several biomarkers for assessing hypoxia are available (Table 1). However, when examined independently, these biomarkers fail to fully capture the complexities and heterogeneity associated with tumor hypoxia (Le and Courter, 2008). Consequently, none of them attain the status of a definitive "gold standard" biomarker for hypoxia.

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Hypoxia-inducible factor

Hypoxia-inducible factors (HIFs) are transcription factors considered the master regulators of cellular response to hypoxia (Bruick, 2003), as they bind to hypoxia response elements (HREs) of most of the genes responsible for cellular adaptation to hypoxic stress (Taylor et al., 2016). HIFs are heterodimers with two different subunits: α and β. The α subunit consists of HIF-1α, HIF-2α, and HIF-3α, and the β subunit only of HIF-1β. HIF-α proteins are regulated by oxygen levels and are only expressed under hypoxic conditions (Srmrnza, 2012). HIF-1β is constitutively expressed and its activity remains unaffected under hypoxic changes (Chu and Jones, 2016). HIF-α is negatively regulated by the von Hippel-Lindau tumor suppressor protein (pVHL) (Iliopoulos et al., 1996). HIF-α proteins contain an oxygen-dependent degradation domain, which gets hydroxylated by oxygen-dependent proline hydroxylase enzymes (PHDs) (Markolovic et al., 2015). pVHL recognizes the hydroxylated sites and promotes HIF-α ubiquitin-proteasome degradation (Salceda and Caro, 1997; Jaakkola et al., 2001). Under hypoxic conditions, the enzymatic activity of PHDs is inhibited, allowing the HIF-α and HIF-β subunits to interact, forming a transcriptional complex that enters the nucleus and binds to HREs, inducing the expression of downstream genes (Wu et al., 2015).

Depending on the biological context, such as tumor growth, infection, or immune response, the regulation of HIF transcription involves different signaling pathways. These encompass PI3K-mTOR (Düvel et al., 2010; Park et al., 2014). Notch (Li et al., 2020), Wnt/β-catenin (Shen et al., 2022), ERK (Wan and Wu, 2016), NF-κB (van Uden et al., 2011). IL-1, and TNF-α (Malkov et al., 2021) pathways. Irrespective of the specific upstream pathway driving HIF activation, the activation of the HIF-1 transcription complex triggers the expression of an array of downstream genes, including VEGF (Cascio et al., 2010; Niklander et al., 2021), angiopoietin-2 (ANGPT2) (Simon et al., 2008), transforming growth factor-β (TGF-β), glucose transporter 1,3 (GLUT1,3), nitric oxide synthase (NOS), matrix metalloproteinases (MMPs), and lactate dehydrogenase (LDHA). In this manner, HIFs play a role in modulating diverse biological processes, including cell proliferation, angiogenesis, autophagy, apoptosis, cell death, immune response, among others (Luo et al., 2022). This explains why hypoxia signaling plays a pivotal role in various human diseases, encompassing both benign and malignant neoplasms, cardiovascular diseases, and neurodegenerative disorders. Still, it is also recognized as vital for normal development and physiological processes, including tooth formation (Fajersztajn and

Table 1. Overexpression of markers under hypoxic conditions.

Markers	Main features
Hypoxia-Inducible Factor (HIF-1)	A protein that plays a central role in the cellular response to hypoxia, regulating the expression of genes involved in adapting to low O_2 conditions.
Erythropoietin (EPO)	A glycoprotein that stimulates the production of red blood cells in the bone marrow in response to hypoxia, promoting tissue oxygenation.
Matrix Metalloproteinases (MMPs)	Some MMPs are induced under hypoxic conditions and play a role in extracellular matrix remodeling.
AMP-Activated Protein Kinase (AMPK)	AMPK is activated in hypoxic situations, playing a role in the regulation of cellular energy metabolism.
NADPH Oxidase (NOX)	NOX activation can occur in response to hypoxia, leading to the production of reactive oxygen species.
Lactate	Lactate accumulation is an indicator of increased anaerobic metabolism, commonly associated with low oxygen conditions.
Galectin	Certain galectins, especially Galectin-1, may be influenced by hypoxic conditions, particularly in the tumor microenvironment.
ADAM-12	A protein that is involved in the formation of invadopodia under hypoxic conditions.
Heparin-binding epidermal growth factor (HB-EGF)	A potent mitogen that participates in the formation of the invadopodia.
NOTCH1	A protein involved in the mechanism of invadopodia formation.
Glucose transporter 1 (GLUT-1)	Overexpression of GLUT-1 is associated with increased glucose uptake, adapting cells to a glycolytic metabolism under hypoxic conditions.
ZEB1	A transcription factor that plays a crucial role in epithelial-mesenchymal transition (EMT). Under hypoxic conditions, there is evidence suggesting that ZEB1 expression can be upregulated.
VEGF, VEGFA, VEGFR-2	VEGF is a family of growth factors, VEGFA is a specific isoform within the VEGF family, and VEGFR2 is the receptor that responds to VEGFA, transmitting signals inside endothelial cells to promote angiogenesis. Hypoxia induces a cellular response that includes the upregulation of VEGF and VEGFA, which, in turn, contributes to the activation of VEGFR2 and the promotion of angiogenesis.
CA IX (Carbonic Anhydrase IX)	CA IX is a hypoxia-inducible enzyme that regulates pH in cells. Its expression is often increased under hypoxic conditions, and it is associated with the adaptation of cells to the acidic microenvironment in tumors.
LOX (Lysyl Oxidase)	LOX is involved in extracellular matrix remodeling. Its expression can be increased under hypoxic conditions, contributing to tissue stiffness, and facilitating tumor progression.
TGF-β (Transforming Growth Factor-beta)	TGF-β is a multifunctional cytokine involved in various cellular processes. Its expression can be influenced by hypoxia and contributes to the regulation of cell growth, differentiation, and immune response.

Veras, 2017; Rombouts et al., 2017).

Hypoxia signaling and normal development

Changes in oxygenation during embryonic development are critical, as they can disrupt both placental and fetal growth, with deleterious consequences on fetal health (Dimasuay et al., 2016), depending on the time, duration, and intensity of the exposure (Huang et al., 2004). During intrauterine life, fetuses are constantly exposed to reduced oxygen levels. They have to develop strategies to guarantee O_2 supply in a low O_2 environment, including increasing heart rate, a large surface area for gas exchange, and higher hemoglobin concentration (Fajersztajn and Veras, 2017) Nevertheless, during the early stages of fetal development, physiological hypoxia is essential to promote normal organogenesis, like that involved in placental establishment (Huppertz et al., 2014), angiogenesis, and hematopoiesis (Dunwoodie, 2009). At early stages of development, the tissues are still immature and do not have the necessary mechanisms to protect themselves against oxidants, therefore low O_2 tension is required to maintain the pluripotent state of embryonic cells (Forristal et al., 2010) and to stimulate the proliferation of cytotrophoblast cells (Tuuli et al., 2011).

Hypoxia has been proposed as an important driving force for normal tooth development. Low O_2 levels induce mesenchymal cells to secrete angiogenic factors to act on neighboring endothelial cells, stimulating the invasion of precursor endothelial cells into the dental papilla, which is vital for the development of a tooth (Rombouts, 2017). Ameloblast differentiation during tooth germ development depends partly on the HIF-2α-Hey2 axis, whose expression depends on low O_2 concentrations (Kimura et al., 2022). Root and periodontium development also occur partly under hypoxic conditions. Low oxygen concentrations induce the expression of HIF-1, which promotes the expression of cementum protein 1 (CEMP1), inducing dental stem cells to differentiate into cementoblasts, increasing cementogenesis (Choi et al., 2014). Hypoxia is also important for pulp regeneration. In injured dental pulp, HIF-1 is the major regulator of angiogenesis by stimulating the paracrine angiogenic activity of dental pulp cells (Aranha et al., 2010).

Hypoxia in the tumor microenvironment

Cancer development is a multistep process that requires the acquisition of functional capabilities crucial for human cells to form malignant tumors, known as the hallmarks of cancer (Hanahan and Weinberg, 2011). Currently, ten hallmarks of cancer have been recognized (eight capabilities and two enabling characteristics): Evading growth suppressors, avoiding immune destruction, enabling replicative immortality, tumor-promoting inflammation, activating invasion and metastasis, inducing or accessing vasculature, genome instability and mutation, resisting cell death, deregulating cellular metabolism, and sustaining proliferative signaling. Additionally, two emerging hallmarks (unlocking phenotypic plasticity and senescent cells) and two enabling characteristics (non-mutational epigenetic reprogramming and polymorphic microbiomes) have been recently proposed (Hanahan, 2022).

Hypoxia, mainly through HIF factors, influences and plays a vital role in several of these hallmarks, namely: sustaining proliferative signaling, deregulating cellular metabolism, and inducing or accessing vasculature (Hanahan and Weinberg, 2011). This translates into favoring tumor vascularization, epithelial-mesenchymal transition (EMT), extracellular matrix remodeling, glucose and lipid metabolism, invasion, drug resistance, and metastasis (Kujan et al., 2017; Wicks and Semenza, 2022).

Head and neck cancer

VEGF is probably the most essential angiogenic factor expressed in solid tumors and is upregulated in oral squamous cell carcinoma (OSCC) (Niklander et al., 2021), the most common form of head and neck cancer. Hypoxia is considered one of the main mechanisms underlying the overexpression of VEGF, as shown by *in vitro* and *in vivo* studies (Shang et al., 2006; Lee et al., 2018). Under hypoxic conditions, HIF-1α binds to hypoxia response elements and regulates changes in the expression of different factors involved in angiogenesis, including VEGF (Bredell et al., 2016), carbonic anhydrase 9 (CAIX), and plasminogen activator inhibitor-1 (PAI-1), which promote neovascularization and tumor spread (Peterle et al., 2018). HIF expression might have prognostic significance, as in OSCC, HIF-1α and HIF-2α expression correlate with clinicopathological parameters, and in *in vivo* mouse models their knockdown inhibited angiogenesis and tumor growth (Zhu et al., 2010).

Moreover, hypoxia constitutes an adverse factor in the management of head and neck cancer, enhances resistance to treatments such as radiation and cytotoxic drugs, and attenuates the probability of attaining a curative outcome (Sumera et al., 2023; Vinciguerra et al., 2023). Hypoxia measurements demonstrate its presence in these cancers, consistently correlating with unfavorable outcomes.

Hypoxia in odontogenic lesions

Odontogenic tumors

The association between hypoxia and head and neck tumors is a topic of significant interest. Tumors frequently encounter areas with inadequate oxygen supply, resulting in a hypoxic microenvironment (Rademakers et al., 2019; Sørensen and Horsman, 2020).

Odontogenic tumors exhibit an elevated proliferation rate of the epithelial parenchyma, leading to the formation of cellular islands through the aggregation of epithelial cells (Ege et al., 2023). As a direct vascular supply to epithelial cells is lacking, these cells depend on nutrients from the surrounding connective tissue for their metabolic requirements. Research on odontogenic tumors and hypoxia has primarily focused on ameloblastoma.

Ameloblastoma

The development and progression of ameloblastoma involves a complex process, with ongoing research efforts aimed at deepening the understanding of this neoplasm. Few articles have been published that establish correlations between diverse proteins and hypoxia, as low-oxygen microenvironments have been linked to the invasion and aggressiveness of ameloblastoma (Sánchez-Romero et al., 2016; da Costa, 2016, 2018; Yoshimoto et al., 2019; de Mendonça et al., 2020; Pereira-Prado et al., 2021; Valladares et al., 2021; AlMuzaini et al., 2022). Ameloblastoma is characterized by a heightened proliferative capacity. This is particularly notable in peripheral cells of the tumor, which have the potential to compromise the oxygen supply of central cells, leading to apoptosis (Valladares et al., 2021). In solid tumors, reduced oxygen concentrations induce hypoxic stress, initiating a cascade of intricate cellular events (Denko, 2008).

HIF-1α represents the most studied marker to understand the implications of hypoxia in the development and progression of ameloblastoma. A summary of the possible effects of hypoxia through HIF-1α can be seen in Figure 1. The overexpression of HIF-1α has been associated with the increased proliferative activity and invasive characteristics of ameloblastic cells (Jain et al., 2023). In general, in solid areas, HIF-1α is expressed in the nucleus, and cystic regions it is expressed both in the nucleus and the cytoplasm, being associated with the potential of invasion and apoptosis (Valladares et al., 2021). Pereira-Prado et al. (2021) demonstrated that HIF-1α and Galectin-3 exhibited a similar staining pattern in ameloblastomas, likely indicating a response to hypoxic stress. This suggests that the interaction between these proteins may play a crucial role in the more aggressive behavior of central ameloblastomas compared with unicystic ameloblastomas. Da Costa and coauthors (da Costa et al., 2016) evaluated the expression of HIF-1α, NOTCH1, ADAM-12, and HB-EGF in ameloblastoma, comparing with calcifying odontogenic cysts and dental follicles. Their results demonstrated the higher expression of these proteins in ameloblastomas, suggesting a possible influence on invadopodium formation and tumor invasiveness (da Costa et al., 2016). Similarly, another study that compared the same lesions (ameloblastoma, calcifying odontogenic cyst, and dental follicle) (de Mendonça et al., 2020), showed ameloblastomas to have higher expression of proteins associated with hypoxia and angiogenesis (i.e., HIF-1α, MMP-2, VEGF, and VEGFR-2). Finally, a recent systematic review that included 13 articles investigating HIF-1α in ameloblastoma, concluded that the significant activity of HIF-1α in the intratumoral sites of ameloblastoma is distinct, and positions it as a candidate for targeted therapy (Jain et al., 2023).

The relationship between hypoxia and apoptosis is complex and involves various molecular pathways. Regarding ameloblastoma, one study described the co-localization of Caspase-3 an apoptosis marker and HIF-1α (da Costa et al., 2018), suggesting their potential contribution to the formation of the cystic areas of the tumor. Under specific circumstances, the protective mechanism initiated by HIF-1α in response to hypoxia proves inadequate for preserving cell viability, leading to a heightened response that culminates in apoptosis through the activation of the caspase cascade.

Valladares et al. (2021) aimed to investigate proapoptotic (p53, Bax, BNIP3) and antiapoptotic (Bcl-2 and GLUT-1) proteins modulated by HIF-1α. Interestingly, the antiapoptotic proteins were expressed in peripheral columnar cells of solid areas, whereas proapoptotic proteins were found in cells of the basal and central layers of the neoplastic islands. Their findings also revealed a significant association between

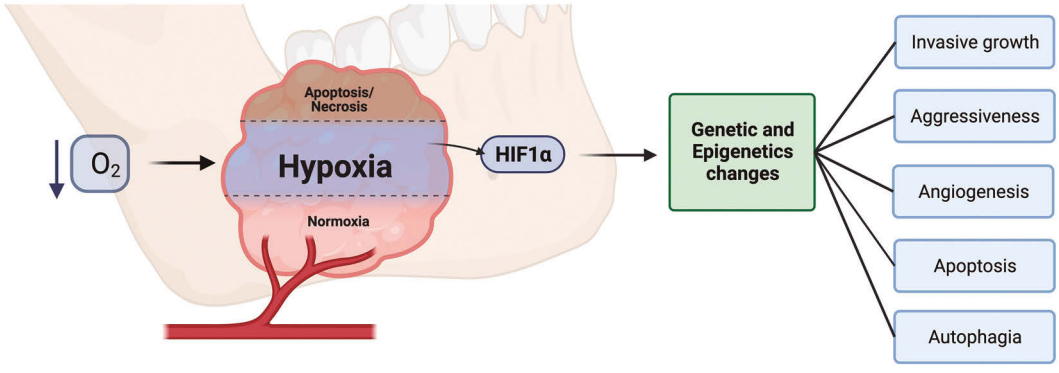

Fig. 1. Graphic summary of the phenotypic advantages that hypoxia, through HIF-1α, may confer to ameloblastoma (created with BioRender.com).

HIF-1α and GLUT-1, suggesting that the positive regulation of GLUT-1 mediated by HIF-1α in hypoxia appears to confer resistance to apoptosis. Sanchez-Romero et al. (2016) similarly analyzed the co-expression of HIF-1α and GLUT-1. All cases of ameloblastoma in their cohort showed cytoplasmatic GLUT-1 staining, potentially associated with growth and local invasion potential. In this sense, membranous expression of GLUT-1 in some tumors could indicate lower glucose demands, as seen with lower levels of proliferation and/or hypoxia.

In response to hypoxia, cells may activate autophagy as a survival mechanism. AlMuzaini et al. (2022) conducted an *in vitro* study under the hypothesis that hypoxia induces autophagia in primary and recurrent ameloblastoma cells. Their results suggested that the hypoxia-mediated autophagic process could help tumor adaptation.

Regarding the malignant transformation of ameloblastomas, an *in vitro* study demonstrated that hypoxia-induced HIF-1α and ZEB1 are critical events (Yoshimoto et al., 2019). The authors discussed the possibility that these proteins could be used as potential biomarkers of ameloblastic carcinoma.

Conclusion

The literature has demonstrated the correlation between hypoxia and ameloblastoma, revealing a discernible link between the heightened expression of hypoxic markers in low oxygen conditions. This association is intricately tied to the tumoral potential for invasion, progression, and malignant transformation. Nevertheless, extant findings are predominantly sporadic, largely stemming from formalin-fixed paraffin-embedded tissue. Ideally, forthcoming investigations should employ molecular methodologies and leverage larger sample cohorts, to elucidate signaling pathways concomitant with the overexpression of hypoxic markers, thereby furnishing a robust foundation for the exploration of targeted therapeutic modalities.

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