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Review

Hypoxia induced EMT: A review on the mechanism of tumor progression and metastasis in OSCC

Joel P. Joseph[a,b], M.K. Harishankar[a], Aruthra Arumugam Pillai[a], Arikketh Devi[a,*]

[a] Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur 603203, India
[b] School of Regenerative Medicine, Manipal Academy of Higher Education, Yelahanka, Bengaluru 560065, India

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ABSTRACT

Hypoxia, a condition of low oxygen tension in tissues, has emerged as a crucial factor in tumor pathophysiology. Hypoxic microenvironment gives rise to altered cellular metabolism and triggers varied molecular responses. These responses promote tumor progression and confer radiation resistance and chemo resistance to tumors. The predominant molecules that are associated with hypoxia research are the hypoxia inducible factors (HIFs). HIFs are known to regulate a large group of genes that are involved in cell survival, proliferation, motility, metabolism, pH regulation, extracellular matrix function, inflammatory cell recruitment and angiogenesis by inducing the expression of their downstream target genes. The process of epithelial to mesenchymal transition (EMT) has been associated with metastasis in cancer. Reports also suggest that hypoxia triggers EMT in several types of cancer including breast cancer, prostate cancer and oral cancer. Oral cancer is a predominant cancer in Central and South East Asia. However, in the recent times, the incidence rates of oral cancer have been increasing in Northern and Eastern Europe as well. This review articulates the role of hypoxia and the associated factors like HIFs in inducing EMT in oral cancer (OSCC).

Introduction

Head and neck cancer encompasses the cancer of the oral cavity, paranasal sinuses, pharynx, and larynx [1,2]. Head and Neck cancer, which develops at the lips, tongue, salivary glands, gingiva, floor of the mouth, oropharynx, buccal surfaces and other intra-oral locations [3], is the sixth most common cancer in the world [4]. The GLOBOCAN 2012 report indicated an estimated 300,400 new cases and 145,400 deaths due to oral cancer, with the highest rates being found in Melanesia and South-Central and Eastern Asia [5,6]. Also, increasing rates of oral cancer are being witnessed in several Eastern and Northern European countries reflecting the ongoing tobacco epidemic [5]. High-risk countries like Pakistan, India, Sri Lanka and Bangladesh have oral cancer incidence rates as high as 25% of all new cancer cases while the low-risk countries like UK have incidence rates of about 3% of all new cancer cases [4]. Of all the subtypes of oral malignancies, 90% constitute the oral squamous cell carcinoma (OSCC) [7], which is a characteristic locally aggressive tumor, whose invasion and metastasis results from the adaptation to the individual microenvironment [8]. For this reason, the 5-year survival rate remains at 50–55% without any change despite aggressive treatment regimens encompassing radiation therapy, chemotherapy and surgery [9]. The upregulation of genes that bring about such invasion and metastasis of tumor is known be enhanced in hypoxic microenvironment. Hypoxia, a reduction in the normal level of oxygen tension in tissues, has been reported to be involved in tumor progression and metastasis of various types of cancer [10]. The role of hypoxia and the associated factors in tumor progression has been elucidated in head and neck cancers [11,12] and particularly in cancer of the oral cavity [8,9,13]. This review articulates the role of hypoxia and the associated factors like hypoxia inducible factors (HIFs) in oral cancer (see Figs. 1 and 2).

Metastasis of oral cancer

Oral malignancies progress through the four stages of cancer and metastasize into distant sites including the hypopharynx, the base of the tongue, and anterior tongue [14]. Metastasis comprises of sequential occurrence of uncontrolled cell proliferation, stimulation of angiogenesis, detachment, motility, invasion into bloodstream and cross-talk with components of the new microenvironment, including parenchymal, stromal and inflammatory cells [2]. Cancer cells detach from the primary site, spread in the tissue, move away through the extracellular matrix, invade the blood stream or the lymphatic system, settle in the microvasculature and finally extravasate from the blood vessel at

* Corresponding author.
E-mail address: adevipradeep@gmail.com (A. Devi).

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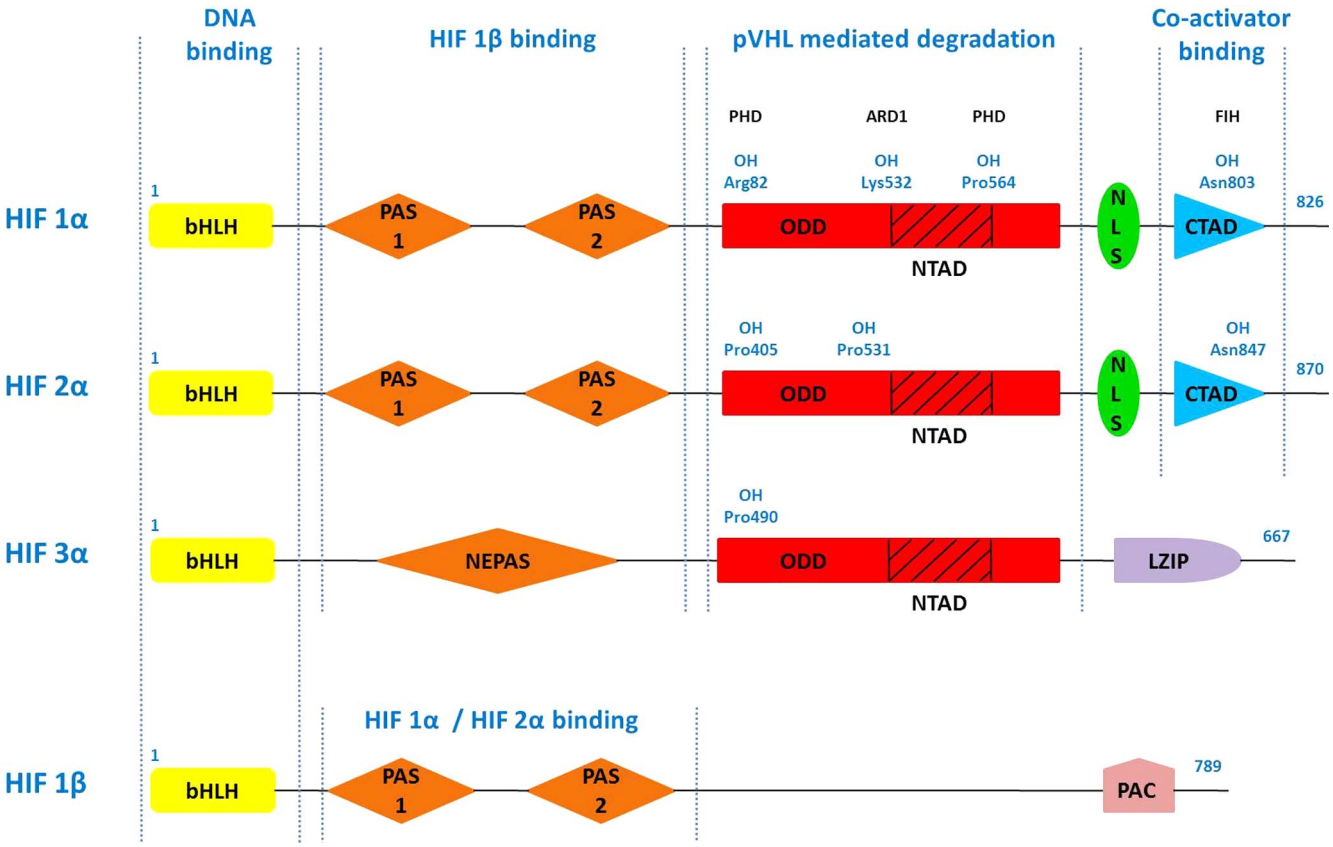

Fig. 1. Domain structure hypoxia inducible factor (HIF) subunits. The structurally important domains include the basic Helix-Loop-Helix (bHLH) domain, Per-Arnt-Sim (PAS) domain, Oxygen Dependent, Domain (ODD), Nuclear Localization Signal (NLS), N-terminal and C-terminal Transactivation Domains (NTAD and CTAD), Leucine Zipper (LZIP) Domain and PAS-associated C-terminal (PAC) Domain. The enzymes that degrade HIFs in normoxic conditions are Prolyl Hydroxylases (PHD) and Factor Inhibiting HIF (FIH).

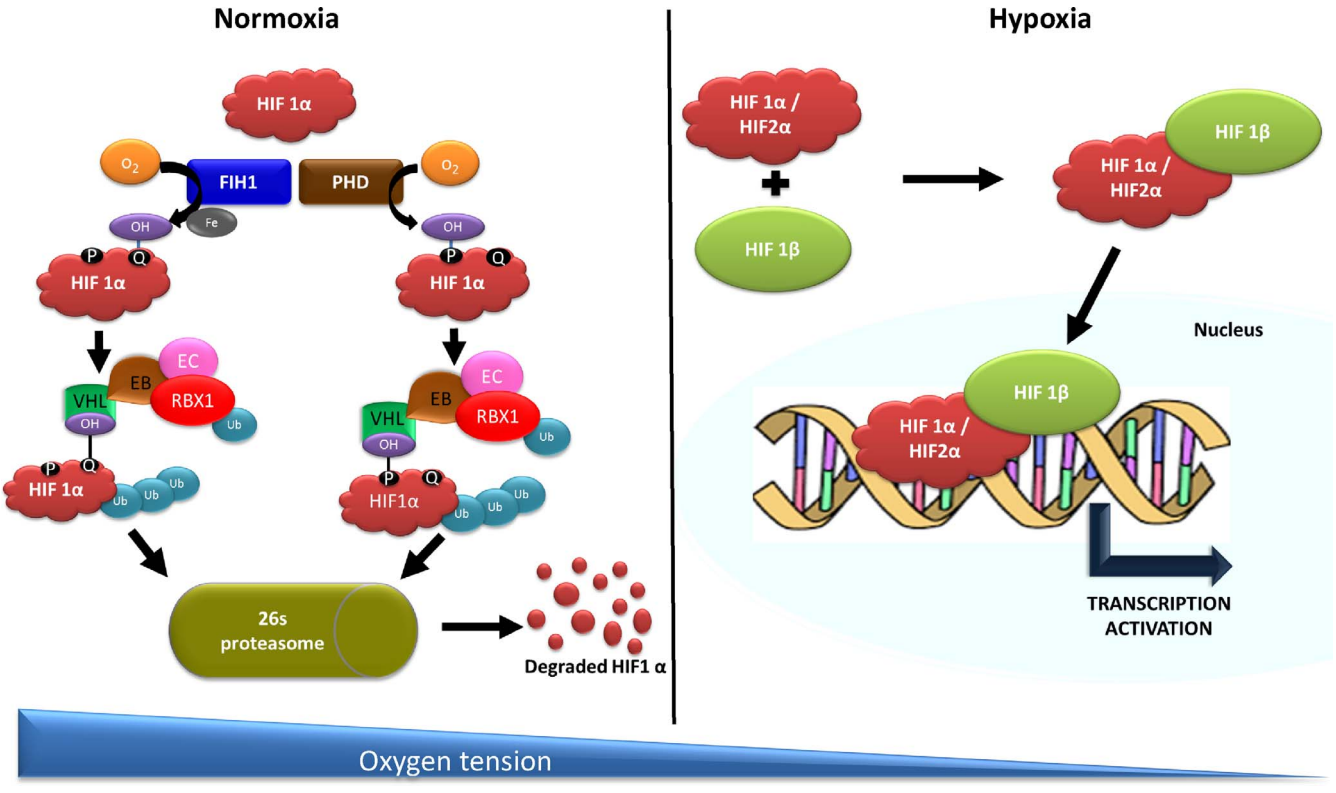

Fig. 2. Degradation of Hypoxia Inducible Factor 1α (HIF 1α) under normoxic condition and the mechanism of action of Hypoxia Inducible Factors (HIFs) under hypoxic conditions. Abbreviations: EB: Elongin B; FIH: Factor inhibiting HIF1; PHD: Prolyl Hydroxylase; RBX1: Ring Box Protein 1; vHL: von Hippel–Lindau tumor suppressor protein; Ub: Ubiquitin.