Role of VEGF in Head and Neck Squamous Cell Carcinomas

Kulsoom Ghias

[1]Department of Biological and Biomedical Sciences, Aga Khan University, Karachi, Pakistan

Head and neck cancers include a heterogeneous group of malignant tumors involving various anatomical sites, such as the oral cavity, oropharynx, hypopharynx and larynx. Predominantly, these tumors are squamous cell carcinomas originating from the epithelium that lines the upper aerodigestive tract. Squamous cell carcinomas of the head and neck (HNSCC) have the sixth highest incidence rate globally [1]. There is considerable geographical heterogeneity in incidence rates that can be attributed to the differences in the distribution of associated risk factors. Despite advances in the treatment, including surgery, radiotherapy and chemotherapy, the 5-year survival is still <50% [1], thus HNSCC is associated with considerable disease-related mortality and treatment-related morbidity [2]. Loco-regional recurrences are seen in 30-40% of patients, distant metastasis in 20-30% of cases, still others present with secondary primary tumors [3]. Tumor site, size, thickness, involvement of adjacent structures, presence of extracapsular spread and perivascular and perineural invasion are some of the factors that have prognostic significance. However, the most important prognostic indicator affecting the overall and disease-free survival is the presence of regional cervical lymph node metastases. This factor alone reduces the survival rates by 50% [4].

HNSCC start as benign squamous cell hyperplasia and progress to dysplasia, carcinoma in situ, and ultimately, invasive carcinoma [2]. The onset and progression of HNSCC is associated with genetic and epigenetic alterations that affect several cellular signaling pathways in the premalignant progenitor cells. Cell cycle de-regulation due to mutations in the p53 and retinoblastoma pathways result in limitless replicative potential, a hallmark of cancer. Somatic mutations in the following pathways have been frequently implicated in HNSCC; the epidermal growth factor receptor (EGFR) signaling pathway, transforming growth factor-β (TGFβ) pathway (affecting cross-talk with the nuclear factor-κB (NF-κB) pathway) and the PI3K–PTEN–AKT pathway (leading to evasion of apoptosis) [1].

All solid tumors induce angiogenesis, usually through production of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), to ensure adequate supply of nutrients and oxygen and disposal of metabolites. Many studies have linked increased VEGF expression with worse HNSCC outcome, including a trend to development of lymph node metastasis. In this issue of JPMS, Torabinia *et al.* show significantly higher expression of VEGF (as assessed by immunostaining) in squamous cell carcinoma of the oral cavity (OSCC), which is clinically one of the most common sites of the origin of head and neck cancers, as compared to dysplastic or normal mucosa. Other studies have also assessed the role of VEGF family members, receptors and other angiogenic factors in OSCC in relation to tumor stage, severity, presence of metastasis, and survival [6]. VEGF-A expression is correlated with advanced stage disease; VEGF-A, VEGF-C, VEGF-D and angiopoietin-1 are positively correlated with lymph node metastasis; and angiopoietin-2 is associated with poor prognosis in OSCC [7]. Mechanistically, VEGF expression is transcriptionally activated by hypoxia-inducible factor-1 (HIF1) as part of the cellular response to hypoxia. The correlation between HIF1α and VEGF has also been shown in OSCC [6]. More recently, high expression of the small heat shock protein $\alpha\beta$-crystallin has been associated with distant metastasis in squamous cell carcinoma and data suggests that this may be linked to $\alpha\beta$-crystallin's role as a molecular chaperone in the proper folding and transport of VEGF [8].

While the mainstay in the treatment of head and neck cancers remains early detection and diagnosis, VEGF-mediated angiogenesis is a viable target for treatment strategies in HNSCC. Bevacicumab, a fully humanized monoclonal antibody against VEGF used in other cancers, has undergone or is currently undergoing trials in combination with chemotherapy, radiation therapy or EGFR inhibitors. Small molecules targeting the VEGF receptor and downstream signaling are also being explored [9]. In preclinical studies and animal models of the disease, cepharanthine, a plant derived alkaloid

has been shown to inhibit VEGF expression and decrease tumor cell growth [6], and mTOR inhibitors have been shown to impair the VEGF-C/VEGF receptor axis and release of soluble VEGF-2 leading to decreased lymphangiogenesis and lymph node metastasis [10].

Identification of specific genetic alterations in each step of HNSCC has led to the development of a model of molecular progression [11] and the identification of possible biomarkers for diagnosis, prognosis and treatment. However, a holistic understanding of the complex disease process of site-specific squamous cell carcinomas of the head and neck region, which are concerted by a number of molecules rather than isolated aberrations, is still needed in order to develop a holistic picture and for better clinical management.

REFERENCES

1. Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. *Nat Rev Cancer* 2011; 11:9-22.
2. Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. *N Engl J Med* 2001; 345:1890-1900.
3. Murar S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis and treatment. *Mayo Clin Proc* 2008; 83:489-501.
4. Shah JP, Andersen PE. Evolving role of modifications in neck dissection for oral squamous carcinoma. *Br J Oral Maxillofac Surg* 1995; 33:3-8.
5. Torabinia N, Razavi SM, Tahririan D. Vascular endothelial growth factor expression in normal, dysplastic and neoplastic squamous epithelium of oral mucosa. *J Pioneer Med Sci* 2014; 4 (3):115-118.
6. De Lima PO, Jorge CC, Oliveira DT, Pereira MC. Hypoxic condition and prognosis in oral squamous cell carcinoma. *Anticancer Res* 2014; 34:605-612.
7. Karatzanis AD, Koudounarakis E, Papadakis I, Velegrakis G. Molecular pathways of lymphangiogenesis and lymph node metastasis in head and neck cancer. *Eur Arch Otorhinolaryngol* 2012; 269:731-737.
8. van de Schootbrugge C, Bussink J, Span PN, Sweep FC, Grenman R, Stegeman H, et al. alphaB-crystallin stimulates VEGF secretion and tumor cell migration and correlates with enhanced distant metastasis in head and neck squamous cell carcinoma. *BMC Cancer* 2013; 13:128.
9. Goerner M, Seiwert TY, Sudhoff H. Molecular targeted therapies in head and neck cancer--an update of recent developments. *Head Neck Oncol* 2010; 2:8.
10. Ekshyyan O, Moore-Medlin TN, Raley MC, Sonavane K, Rong X, Brodt MA, et al. Anti-lymphangiogenic properties of mTOR inhibitors in head and neck squamous cell carcinoma experimental models. *BMC Cancer* 2013; 13:320.
11. Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, et al. Genetic progression model for head and neck cancer: implications for field cancerization. *Cancer Res* 1996; 56:2488-2492.