REVIEW ARTICLE

HER GENE FAMILY AS A THERAPEUTIC TARGET IN ORAL SQUAMOUS CELL CARCINOMA

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ABSTRACT

Despite recent advancement in pathogenesis and management of disease, oral cancer remains the most common human malignancy, worldwide. The aggressive behavior of OSCC is a challenge for new treatment modalities for primary as well as metastatic lesions. HER receptors play an important role in the normal physiological process as well as in the development of many cancers including oral squamous cell carcinoma. An electronic article search was done through PubMed, Google Scholar and Medscape were used for an electronic search of articles, using the following keywords: oral cancer, EGFR, Her/2, Her/3 and Her /4. All types of articles were included. The aim of this review is to outline the current knowledge on the role of HER receptors in the progression of OSCC in order to use them as a therapeutic target in high risk OSCC patient and to prevent them from aggressive surgeries causing post-operative morbidity.

KEY WORDS: Oral squamous cell carcinoma, HER1, HER-2, HER-3 and HER-4, over expression, Immunohistochemistry.

INTRODUCTION

Worldwide, Oral squamous cell carcinoma (OSCC) is classified as sixth most common cancer [1], contributing to about 5% of all cancers in the Western World [2], whereas, OSCC is the main cause of mortality and morbidity in South East Asian countries [3]. The cultural practices like tobacco and betel quid chewing raises the prevalence of OSCC up to 40% in India and 10% in Pakistan [4]. Despite extensive research into the pathogenesis and management of oral squamous cell carcinomas, the five-year survival rate in the last 25 years, remains same [5].

The role of Biomarkers before cancer diagnosis is the risk assessment and screening, along with providing support in diagnosis and after diagnosis, for monitoring therapy, selecting additional therapy and detecting recurrence [6]. Numerous markers are identified related to tumor grading and staging as well as clinical course of the disease for prognosis. Mutation of the tumor suppressor gene p53, amplification of the proto-oncogene like cyclinD1,7-13 and over expression of the tyrosine kinase receptor that is, epidermal growth factor14-17 have been associated with poor prognosis [7].As an alternative, vaccine therapy targeting Her2/neu, a growth factor receptor has been actively researched to improve survival [8].
ErbB is also known as HER, is a family of proto-oncogenes, tyrosine kinase growth factor receptors. It is responsible for cell proliferation and differentiation. HER family comprises four receptors; EGFR (HER1 or ErbB-1), ErbB-2 (HER-2 or neu), ErbB-3 (HER-3) and ErbB-4 (HER-4), and their over-expression is associated with progression of tumor [9,10].

An electronic article search was done using key words EGFR, Her/2, Her/3 and Her /4 on Google Scholar, PubMed and Medscape. All types of articles including original, review, case reports, clinical observational cohort studies and randomized controlled trials were included. About 100 abstracts of related articles were reviewed first followed by selection of 70 abstracts. Full text articles of these were included in this review. The purpose of this review is to outline the role of HER receptors in carcinogenesis of OSCC in order to exploit them as therapeutic target in high risk OSCC patient and to prevent them from aggressive surgeries causing post-operative morbidity.

ErbB/ HER RECEPTORS

All ErbBs includes an extracellular ligand- binding domain, a single membrane-spanning region, and a cytoplasmic protein tyrosine kinase domain. There activation is controlled by the ligands which upon proteolysis of ectodomains, leads to shedding of soluble growth factors [11,12]. There are three groups of

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ErbB specific ligands. The first group (ErbB1) bind specifically to ErbB-1 receptor and include EGF, amphiregulin(AR), and transforming growth factor-α (TGF-α). The second group has dual characteristics of binding to ErbB-1 as well as ErbB-4 and includes betacellulin(BTC) Heparin binding EGF(HB-EGF) and epiregulin (EPR). The third group consists of the neuregulins which has two subgroup depending on their binding capacity. Those binding to ErbB-3 and ErbB-4 are NRG-1 and NRG-2 while ErbB-4 binds NRG-3 and NRG-4. [13].(Figure-1)

The binding of ligands to ErbB receptors form homo and heterodimers, which activate phosphorylation and intrinsic kinase domain in the cytoplasmic tail, resulting in stimulation of intracellular pathways. No direct ligand to ErbB2 has been revealed as yet. ErbB3 having no intrinsic tyrosine kinase, dimerizes with another ErbB receptor [14,15]. Moreover, cancer patients with altered ErbB receptors show more aggressive clinical presentation [16].

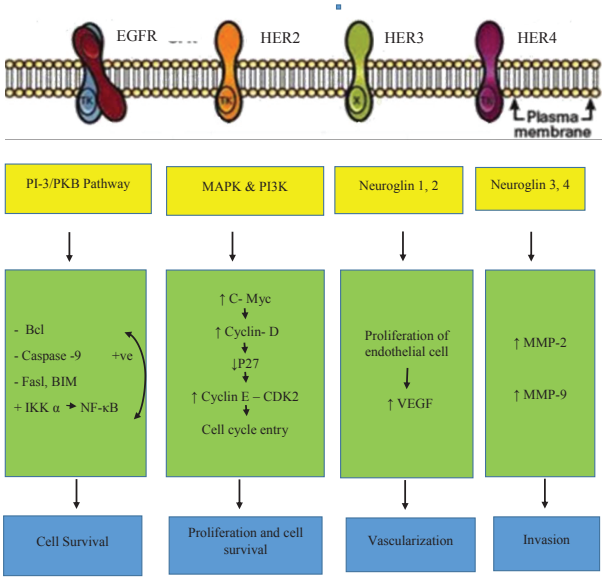

Figure 1: Role of HER family in carcinogenesis HER 1 Receptor plays a role in cell survival by activating PI-3/PKB pathway while HER 2 receptor helps in cell proliferation and migration by activating MAPK and PI3K pathway. HER 3 and HER-4 promote neovascularization and invasion through neuroglins respectively.

ROLE OF HER RECEPTORS IN ORAL SQUAMOUS CELL CARCINOMA

EGFR/HER-1 Receptor

EGFR has several structural variants observed in human malignancies. Wikstrand et al state that, the most frequently detected variant of EGFR is EGFvIII, which is expressed in 42% of oral tumors [17]. Several studies indicate that the incidence of EGFR mutations in oral carcinoma differ between ethnic groups, incidence being more in Asians (7%) in comparison to white caucasian (4%) [18,19]. Immunohistochemical studies of EGFR protein staining is observed in 42-58% of OSCC cases[20]. However conflicting results were found in one of the study reporting that EGFR positive lesions present as low grade tumors and show no association with patient outcome. [21]

Monoclonal antibodies directed against this receptor might prove to be effective therapeutic agents [22]. When oral squamous carcinoma cells were pre-treated with EGF, it resulted in increased sensitivity to radiation in relation to the number of EGFRs on their surfaces. Antibody named Cetuximab was introduced having effect on tumor cells. It induces autophagy in several cancer cell lines, including oral cancer via inhibition of EGFR signaling.

HER-2 Receptor

The HER-2/neu oncogene is found on the short arm of chromosome 17 [23]. The overexpression of HER-2 was found to be associated with numerous types of human cancers like breast cancer, lung cancer, gastric cancer and salivary cancer [24]. However, rate of Her-2 in OSCC is reported to be controversial, with reports of overexpression in 3-41% of cases (20). In a study done by Khan et al (2002) out of 67 OSCC patients 78% were negative for membrane staining, while only 17% showed positive results with no significant association between HER-2/neu positivity and primary tumor site, T stage, N stage, tumor grade, recurrence, margin status, sex, race and age [25]. Craven et al demonstrated HER-2/neu overexpression in 46% of OSCC patients by IHC but do not found any correlation of overexpression with clinical parameters [26]. Beckhardt et al conducted a comprehensive evaluation of HER-2/neu in OSCC patients revealing only 6 of 38(16%) OSCC tissue sections with HER-2 oncoprotein over expression [23].

Stoicanescu et al (2013) analyzed HER-2 receptor protein expression by immunohistochemistry and revealed that 76.76% cases were negative, 5.17% were 1+,14.65% cases 2+ and only four cases were 3+[27]. Other studies have also proven that HER-2 has no significant role in the progression of cancer [28,29].Moreover, two studies by Riveire et al failed to demonstrate enhanced HER-2 transcription on northern blot or enhanced protein expression in IHC in their series of head and neck SCC [30,31]. It can be concluded that HER2/neu has no significant role in OSCC and cannot be used as potential target for anticancer therapy.

HER-3 Receptor

HER-3 is normally present in squamous epithelium of head and neck squamous cell carcinoma, oropharynx, esophagus, and tongue, related to increased metastatic potential and poor survival rates [32,33].
Lapatinib, which is a dual EGFR/HER2 reversible inhibitor showed sensitivity to the "head and neck

squamous cell carcinoma" cell lines [34]. In OSCC gefitinib being EGFR inhibitor showed significant resistance to HER2 and HER3 expression but not to cetuximab. Pertuzumab which is the blend of gefitinib and the HER2-HER3 dimerization inhibitor provide increased growth inhibition than gefitinib alone [35]. The process by which HER3 is sensitive to lapatinib but resistant to gefitinib is not identified yet. This concludes that HER3 expression have a significant role in carcinogenesis and it would be a rational target for anticancer therapy.

Her-4 Receptor

Her-4 is expressed in many cancer cells including prostate cancer, lung cancer, colon cancer, cervical cancer, and stomach cancer. Its role in tumor development is not clear yet, as it might have prognostic significance in combination with other receptors [36]. The role of HER-4 in OSCC is poorly understood. It does not seem to be over expressed in OSCC which is also supported by a study conducted by Ekberg et al in 2004, concluding that HER 4 might not be suitable for macromolecular targeting therapy [32].

CONCLUSION

The HER- family is associated with many intracellular pathways like cell proliferation, differentiation, migration and survival. Genetic alterations like gene amplification, deletion or co/over-expression of these receptors can lead to tumor progression.HER-1 being overexpressed in 42-58% of cases have an important role not only in early diagnosis but also in prognostic evaluation and treatment planning. This could prove to be an effective therapeutic agent against OSCC patients. The over expression of HER-2 in OSCC varies from 3-41% and does not co-relate well with clinic-pathological parameters, and cannot be regarded as a potential biomarker for treatment modalities. On the other hand, HER-3 has increased metastatic potential and poor survival, so it could be a target for anti-cancer therapy. The role of HER-4 has not yet been explored in OSCC

REFERENCES

1. Shah JP, Gil Z. Current concepts in management of oral cancer-surgery. Oral oncol.2009;45(4-5):394-401
2. Boyle P, Levin B. World Cancer Report 2008. Lyon: International Agency for Research on Cancer; 2008
3. Parkin DM, Laara E, Muir CS. Estimates of the worldwide frequency of sixteen major cancers in 1980. Int J Cancer.1988; 41(2):184-97.
4. Grimminger CM, Danenberg PV. Update of prognostic and predictive biomarkers in oropharyngeal squamous cell carcinoma: a review. Eur Arch Otorhinolaryngol 2011; 268 :5-16.
5. Khan MA, Saleem.S, Shahid SM, Hameed A, Qureshi NR, Abbas Z. Prevalence of oral squamous cell carcinoma (OSCC) in relation to different chewing habits in Karachi, Pakistan. Pak. J. Biochem. Mol. Biol. 2012; 45(2): 59-63
6.Markopoulos AK: Current Aspects on Oral Squamous Cell Carcinoma. Open Dent J.2012;6:126-130
7. Ludwig JA, Weinstein JN. Biomarkers in cancer staging, prognosis and treatment selection. Nat Rev Can 2005; 5(11): 845-56.
8. Chen SA, Tsai MH, Wu FT, Hsiang A,Chen YL, Lei HY et al. Induction of Antitumor Immunity with Combination of HER2/neu DNA Vaccine and Interleukin 2 Gene-modified Tumor Vaccine. Clin Cancer Res.2000; 6(11):4381-4388.
9. De Vicente JC, Esteban I, Germanà P, Germanà A, Vega JA. Expression of ErbB-3 and ErbB-4 protooncogene proteins in oral squamous cell carcinoma: a pilot study. Med Oral 2003; 8(5):374-81.
10. Fong Y, Chou SJ, Hung KF, Wu HT, Kao SY. An investigation of the differential expression of Her2/neu gene expression in normal oral mucosa, epithelial dysplasia, and oral squamous cell carcinoma in Taiwan. J Chin Med Assoc 2008; 71(3):123-7.
11. Peles E, Yarden Y. Neu and its ligands: from an oncogene to neural 3factors. Bioessays. 1993; 15(12): 815–824
12. Riese DJ 2nd1, Stern DF. Specificity within the EGF family/ErbB receptor family signaling network. Bioessays.1998; 20(1): 41–48.
13. H.Ogiso, Ishitani R, Nureki O, Fukai S,Yamanaka M, Kim J et al. Crystal structure of the complex of human epidermal growth factor and receptor extracellular domains. Cell. 2002; 110: 775-787.
14. Guy PM, Platko JV, Cantley LC, Cerione RA, Carraway KL. Insect cell-expressed p180erbB3 possesses an impaired tyrosine kinase activity, Proc. Natl. Acad. Sci. USA.1994; 91(17):8132–8136.
15. Kim HH, Vijapurkar U, Hellyer NJ, Bravo D, Koland JG. Signal transduction by epidermal growth factor and heregulin via the kinase-deficient ErbB3 protein. Biochem. J. 1998; 334 (1): 189–195.
16. Hynes NE, MacDonald G. ErbB receptors and signaling pathways in cancer. Curr Opin Cell Biol. 2009;21(2):177-84
17. Wikstarnd CJ, Reist CJ, Archer GE, Zalutsky MR, Bigner DD. The class III variat of the epidermal growth factor receptor EGFRvIII: characterizaiton and utilization as an immunotherapeutic target. J neurovirol .1998 ;4(2) : 148-158.
18. Ribeiro FA, Noguti J, Oshima CT, Ribeiro DA. Effective Targeting of the epidermal growth factor receptor (EGFR) for treating oral cancer: A Promising Approach 2014; 34(4): 1547-1552.
19. Yano S, Kondo K, Yamaguchi M, Richmond G, Hutchison M, Wakeling A, et al. Distribution and function of EGFR in human tissue and the effect of EGFR tyrosine kinase inhibition. Anticancer Res.2003;23(5):3639–50.
20. Rautava J, Jee KJ, Miettinen PJ, Nagy B, Myllykangas S, Odell EW et al. ErbB receptors in

developing dysplastic and malignant oral epithelia. Oral Oncol. 2008; 44(3): 227-235.
21. Bernardes VF, Gleber-Netto FO, Sousa SF, Rocha RM, Aguiar MC. EGFR status in oral squamous cell carcinoma : comparing immunohistochemistry, FISH and CISH detection in a case series study. BMJ open 2013;3(1): 1-18.
22. Rubin I. Yarden Y. The basic biology of HER-2 . Ann Oncol. 2001; 12(1): 3-8.
23. Beckhardt RN, Kiyokawa N, Xi L, Liu TJ, Hung MC, el-Naggar AK et al. HER-2/neu oncogene characterization in head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 1995; 121(11): 1265-1270.
24. Angiero F, Sordo RD, Dessy E, Rossi E, Berenzi A, Stefani M et al. Comparative analysis of c-erbB-2(HER-2/neu) in squamous cell carcinoma of the tongue: does over expression exist? And what is its correlation with traditional diagnostic parameters?. J Oral Pathol Med 2008; 37(3):145-150.
25. Khan AJ, King BL, Smith BD, Smith GL, DiGiovanna MP, Carter D et al. Characterization of the HER-2/neu Oncogene by Immunohistochemical and Fluorescence in situ Hybridization Analysis in oral and oropharyngeal Squamous cell carcinoma. Clin Cancer Res. 2002 ;8(2):540-8.
26. Craven JM, Pavelic ZP, Stambrook PJ, Pavelic L, Gapany M, Kelley DJ. Expression of c-erbB-2 gene in human head and neck carcinoma. Anticancer Res 1992;12(6): 2273-2276.
27. Stoicanescu D. Andreescu N. Belengeanu A. Meszaros N. Cornianu M. Assessment of p53 and HER-2/neu genes status and protein products in oral squamous cell carcinomas. Rom J Morphol Embryol 2013; 54(4): 1107-1113.
28. Seifi S,Shafaie S. HER2/neu and αSMA Expression in Oral Squamous Cell Carcinoma.Shiraz Univ Dent J 2011; 12(1):11-18.
29. Sardari Y, Pardis S, Tadbir AA, Ashraf MJ, Fattahi MJ, Ebrahimi H. HER-2/neu Expression in head and neck squamous cell carcinoma patients is not significantly elevated. Asian Pac J Cancer Prev. 2012;13(6):2891-6.
30. Rivière A, Becker J, Löning T. Comparative investigation of c-erbB-2/Neu -2 expression in head and neck tumor and mammary cancer. Cancer. 1991;67(8):2142-9.
31. Riviére A, Wilckens C, Löning T. Expression of c-erbB-2 and c-myc in squamous epithelia and squamous cell carcinoma of the head and neck and the lower female genital tract. J Oral Pathol Med 1990; 19(9): 408-413.
32. Ekberg T, Nestor M, Engström M, Nordgren H, Wester K, Carlsson J et al. Expression of EGFR, HER-2, HER-3 and HER-4 on metastatic squamous cell carcinomas of the oral cavity and base of tongue. Int J Oncol. 2005;26(5):1177-85.
33. Jiang N. Saba NF. Chen ZG. Advances in targeting HER-3 as an anticancer therapy. Chemother Res Pract. 2012;2012:304-313
34. Wilson TR, Lee DY, Berry L, Shames DS, Settleman J. Neuregulin-1mediated autocrine signaling underlies sensitivity to HER2 kinase inhibitors in a subset of human cancers. J.Cancer Cell 2011;20(2): 158–172.
35. Erjala K, Sundvall M, Junttila TT, Zhang N, Savisalo M, Mali P. Signaling via ErbB2 and ErbB3 associates with resistance and epidermal growth factor receptor (EGFR) amplification with sensitivity to EGFR inhibitor gefitinib in head and neck squamous cell carcinoma cells.J. Clin Cancer Res. 2006;12(13):4103-11.
36. Srinivasan R, Poulsom R, Hurst HC,Gullick WJ: Expression of the c-erbB-4/HER4 protein and mRNA in normal human fetal and adult tissues and in a survey of nine solid tumour types. J Pathol.1998;185: 236-245.