Role of Epidermal Growth Factor (EGFR) in Oral Cancer

Abstract:
Oral cancer is a pronounced disease and has the sixth-highest incidence among all the cancers occurring worldwide. Among various markers found in oral squamous cell carcinoma, Epidermal Growth Factor (EGFR) is of most prognostic significance. But no established criterion is universally used to evaluate EGFR expression. EGFR is known to perform a significant role in oral cancer development and its overexpression dictates the poor clinical course of cancer. It is considered to be not only a useful prognostic biomarker but also a promising therapeutic target and in cancer treatment. Stimulation of EGFR enhances the processes of cancer including increased cell division, neovascularization, invasion/metastasis, and escape from apoptosis. Increased EGFR levels are also observed in other cancers of the body. EGFR detection in OSCC can fulfil multiple roles in cancer diagnostics like the early stage, assessing the prognosis and treatment plan. The EGFR is a proto-oncogene, is activated at the cell membrane surface by transforming growth factor-α serves to advance cellular proliferation in cancer tissue. The literature demonstrates that that EGFR is an important target for anti-cancer drugs in an advanced stage of head and neck cancers. Hence, understanding of EGFR is important to learn the development cascade of cancer.
Keywords: Oral Cancer, Carcinoma, EPFR, Prognosis, Biomarker.

Introduction:

Oral cancer is a pronounced disease and has the sixth-highest incidence among all the cancers occurring worldwide. (1) It comes under head and neck region cancers domain, and of all these, they comprise about 85% of that category (2). The International Agency for Research on Cancer and World Health Organization reported that in India, 652 723 (accounts for 56.4% of all cancers in the country) many new cases of oral cancer have been diagnosed in the year 2018. (3). Despite development and advances in treating cancer, there is still no change in the survival rate of cancer patients, thus a thorough knowledge of the alterations at the molecular level may aid in finding a relevant novel predictive factors which can precisely predict the performance of the illness (4,5). The stage of invasion and metastasis cancer progression is related to unwanted clinical outcomes and constitute to be an important difficult barrier to a successful outcome. Epidermal growth factor (EGF) induced signalling has found to be associated with tumour invasiveness and metastatic behaviour. (6). The receptors (EGFR, ErbB-1, or HER-1) of EGF play a crucial role in cell growth and differentiation in normal tissues as well as in carcinogenesis and the development of the malignant disease. (7). Among various markers that are relevant in oral squamous cell carcinoma (OSCC), EGFR is most beneficial to prognosticate and also to design the treatment protocol. But no established criterion is universally used to evaluate EGFR expression. EGFR is known to perform a significant role in oral cancer development and it is overexpression is associated with the poor clinical course of cancer. (8,9,10). It is considered to be not only a useful prognostic biomarker but also a promising therapeutic target and is used in cancer treatment (11). Stimulation of EGFR enhances the processes of cancer including increased cell division, neovascularization, invasion/metastasis, and escape from apoptosis (12, 13). Increased EGFR levels are also observed in other cancers of the body (12,14). EGFR detection in OSCC can fulfil multiple roles in cancer

diagnostics like the early stage, assessing the prognosis and treatment plan (15). The EGFR is a proto-oncogene, is activated at the cell membrane surface by transforming growth factor-α serves to advance cellular proliferation in cancer tissue (16). The literature demonstrates that that EGFR is an important target for anti-cancer drugs in an advanced stage of head and neck cancers. (17). Hence, understanding of EGFR is important to learn the development cascade of cancer.

The family of EGF and its Receptors:

EGF was first discovered by Dr Stanley Cohen during his studies on Nerve Growth Factor in the 1960s.(18). It is a single-chain polypeptide consisting of 53 amino acids and curently known as prototype of group 1 EGF family (19,20,21). It binds on its receptor known as EGFR. A glycoprotein EGFR (170-kDa) is a monomer which is present in a variety of body tissues and is responsible for the survival and growth of cells as well as in stimulating multiple signalling cascades (22). It is a tyrosine kinase receptor located at the cell membrane which has been shown to involve in both normal and abnormal proliferation of epithelial tissues and by a gene located on chromosome 7p12.(23,24) EGFR is a member of the ErbB family of Receptor Tyrosine kinase, which includes four structurally similar members: EGFR (ErbB1, HER1), ErbB2 (neu, HER2), ErbB3 (HER3) and ErbB4 (HER4) (25, 26).

The receptor undergoes conformation after binding of specific polypeptide ligands, which undergoes homo- or hetero-dimerization with other EGFR molecules or with other HER family members respectively which results in activation of its intrinsic tyrosine kinase activity. This results in activation of signalling pathway within the cells and subsequently, phosphorylation of EGFR activates multiple biological processes leads to apoptotic inhibition, stimulates the division of cells and promotes neovascularization, as well as tigers the metastatic power of cancerous cells. (27,28) Activated EGFR stimulates several cascades pivotal for the survival and progression of.

Expression of EGFR in OSCC:

The nature EGFR overexpression differs from cancer to cancer and 80-90% of its overexpression is been reported in OSCC (29). In oral squamous cell carcinoma, overexpression of EGFR associates with poor clinical outcomes and it has been observed to be a critical analytical and predictive marker (17). Though its amplification has also been observed, the nature of this overexpression may be due to an increase in the transcription of EGFR (30). In a study on the gene amplification, microRNA (mRNA) expression and protein overexpression of EGFR, it was observed that there was a remarkable correlation between gene amplification and mRNA expression, whereas protein overexpression did not associate with mRNA expression suggestive of the fact that EGFR expression is not regulated transcriptionally (31). Other studies have proven that the expression of EGFR increases considerably with advancement from dysplastic lesions to OSCC (32, 33). It is also increased in the normal epithelial cells adjacent to oral cancer compared with normal tissue of healthy patients and is called “field cancerization” (30). In normal tissues, the EGFR is limited to the basal layer while it wide spreads in all the layers of the epithelium in oral cancer tissue (34). Some studies have observed that pEGFR expression was in association with the expression of E-cadherin protein (35). Reduction in E-cadherin expression increases EGFR in keratinocytes (36) and E-cadherin expression is found to be decreased in oral cancer in another study (37). EGFR expressing oral cancer exhibit pathological characteristics of more aggression which may be attributable to the

activation of different signalling pathways that control various biological processes in cancer progression (38).

EGFR Signalling in OSCC:

EGF binds to its receptor, the EGF receptor (EGFR, ErbB1), activates tyrosine kinase and leads to downstream signalling pathways controlling cell proliferation, differentiation, survival, or motility. (39, 40). EGF and its receptor are linked with cancer development and metastasis through 1) Enhancing cell division and migration through EGFR-Ras/Raf/MEK/ERK and EGFR-PI3K/AKT pathways, 2) Limiting the EGFR in the nucleus to promote cell propagation, 3) Down streaming the autophagy activity, 4)activation of several matrix metalloproteinases facilitating cancer invasion 5) EGF-mediated reduction of mRNAs restraining oncogenic transcription factors (41). The EGFR signal stabilizes b-catenin, decreases the membrane-bound b-catenin, enhances b-catenin nuclear accumulation by phosphorylated regulation and also induces the mesenchymal cell morphology. Thus the dysregulation of b-catenin mediated via EGFR signalling leads to overexpression of oncogenes and promotion of neoplastic growth (42). Stimulation of EGFR promotes the migration of cancer via induction of EMT-like change and MMP-9 mediated degradation of E-cadherin (43). The activation of the PI3K pathway in cancer has been demonstrated to develop resistance to treatment which ultimately leads to the development of cancer disease. (44,45) EGFR upregulates the PI3K signalling that further activates the IA PI3Ks (46). The mutant form of EGFR activates and potentiates the PI3K signalling and plays its role in carcinogenesis (47). The RAS signalling is a crucial pathway in facilitating the biological reaction of the EGFR. ERK MAPK (mitogen-activated protein kinase) interaction leads to responses like growth, proliferation, differentiation, migration, and inhibition of apoptosis in cancer (48). EGFR pathway induced PDK1 expression of fibronectin, MMPs, and Rac1/ cdc42. This shows that the expression of fibronectin and MMPs is one of the downstream signalling mechanisms that mediate lactate-induced metastasis (49). EGF also induces rapid tyrosine dephosphorylation of focal adhesion kinase (FAK) which is associated with downregulation of its kinase activity (50). Undoubtedly, the localization of the EGF and its receptor EGFR provides a better knowledge of its role in cancer as well as prognosis and treatment.

Targeting EFGR in Oral Cancer:

Treatment of OSCC includes single-modality surgery, radiotherapy or combinations of these modalities with or without chemotherapy and/or target agents (51). As mentioned earlier, increased expression of EGFR and destructive actions of cancer cells, monoclonal antibodies concentrating in contrast to this receptor may observe to be an efficient agent (52). Cetuximab is an anti-EGFR antibody has demonstrated to encourage autophagy in many cancers in-vitro, including OSCC (53,54). Erlotinib is another orally-active potent, selective inhibitor of the EGFR tyrosine kinase. Erlotinib in combination with cisplatin has achieved a success rate of 21% phase I/II trial in patients reporting with recurrent cases of oral cancer (55). Inhibition of EGFR signalling plays a pivotal role in cancer development either by connecting to the extracellular domain or by targeting the portion which is inside the cell and has TKA. Thus, EGFR should be considered not only as useful diagnostic and prognostic but also a promising therapeutic target (53). Studies on different diagnostic techniques and immunochemical biomarkers (56-61) in oral cancer were reported.

Conclusion:

This review focused to present a health-giving approach of EGF and EFGR in oral cancer, its role, its expression, its signalling pathway and targeting it using chemotherapeutic

agents. EGFR overexpression has been well reported in oral cancer, but still, its mechanism and significance in the biology of oral malignancies are yet to be thoroughly defined. Increased expression of EGFR in OSCC may be suggestive of its positive role in the proliferation and differentiation of tumour cells and prognostic significance regarding disease-free survival. Detection of EGFR as a biomarker is a key to identify any oral malignant transformation.

References:

1. Jerlucia Cavalcanti das Neves, Livia Soraya Toledano, Fabiana Moura da Motta Silveria, Paulo savior Angeiras de Goes. International Journal of Clinical Medicine 2015; 6:105-111
2. Oral cancer Foundation. https://oralcancerfoundation.org/facts (accessed 16.11.2014)
3. International Agency for Research on Cancer/World Health Organization. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (accessed 16.11.2014).
4. Magrath I, Litvak J. Cancer in developing countries: opportunity and challenge. J Natl Cancer Inst. 1993; 85:862-74. Doi: 10.1093/jnci/85.11.862.
5. Sciubba JJ. Oral cancer. The importance of early diagnosis and treatment. Am J Clin Dermatol. 2001; 2:239-51. Doi: 10.2165/00128071-200102040-00005.
6. Ashish Mahendra, Balasundari Shreedhar, mala Kamboj, Arun Singh, Abhishek Singh, ashutosh Agrawal, sachin kumar, Arpita kabiraj. Journal of Dental Surgery 2014 Arteaga C. Targeting HERI/EGFR: a molecular approach to cancer therapy. Semin Oncol. 2003; 30:3-14.
7. Arteaga C. Targeting HERI/EGFR: a molecular approach to cancer therapy. Semin Oncol. 2003; 30:3-14.
8. Sheu JJ, Hua CH, Wan L, et a. Functional genomic analysis identified epidermal growth factor receptor activation as the most common genetic event in oral squamous cell carcinoma. Cancer Res 2009; 69:2568-76.
9. Lai SY, Koppikar P, ThomasSM et al. Intramural epidermal growth factor receptor antisense DNA therapy in head and neck cancer: first human application and potential antitumor mechanisms. J Clin Oncol 2009; 27:1235-42.
10. Temam S, Kawaguchi H, El-Naggar AK, et al. Epidermal growth factor receptor alterations correlate with poor clinical outcome in patients with head and neck squamous cancer. J Clin Oncol 2007; 25:2164-70.
11. Yuichi Ohnishi, Hiroki Yyasui, Masami Nozaki, Masahiro Nakajima. Japaneses Dental Science Review 2018; 54: 88-103.
12. Wells A. The epidermal growth factor receptor (EGFR) – a new target in cancer therapy Signal. 2000; 1:4-11.
13. Woodburn JR. The epidermal growth factor receptor and its inhibition in cancer therapy. Pharmacol The. 1999; 82:241-250.
14. Baseloa I. New technologies in epidermal growth factor receptor-targeted cancer therapy. Signal 2000; 1:12-21.
15. Weigum S, Floriano P, Christodoulides N and McDevit J: Cell based sensor for analysis of EGFR biomarker expression in oral cancer. Lab Chip 7:995-1003, 2007.
16. Lim SC, Zhang S, Ishii G, Endoh Y, Kodama K, Miyamoto s, Hayashi R, Ebihara S, Cho JS, Ochiai A. Predictive markers for… cervical metastasis in stage I and II invasive squamous cell carcinoma of the tongue. Clin Cancer Re5 2004 Jan; 10(1 Pt 1):166-172.
17. Gabriella Aquino, Giuseppe Pannone, Angela Santoro, Giuseppina Liguori, Renatofranco.

18. Navis, Adam R. Epidermal growth factor. Embryo project encyclopedia (2007-10-30). ISSN: 1940-5030 http://embryo.asu.edu/handle/107761719.
19. Gregory H. Isolation and structure of urogastrone and its relationship to epidermal growth factor. Nature. 1975; 257:325-327.
20. Harris RC, Chung E, Coffey RJ. EGF receptor ligands. Exp Cell Res. 2003; 284:2-13.
21. Schneider MR, Wolf E., Wolf E. The epidermal growth factor receptor ligands at a glance. Cell Physiol.2009; 218:460-466.
22. Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related malignancies. Cnl Rev Oncol Hematol 1995; 19:183-232.
23. Singla S, Singla G, Zaheer S, Rawat DS, Mandal AK. Expressin of p53, epidermal growth factor receptor, c-erbB2 in oral leukoplakias and oral squamous cell carcinomas. J Can Res Ther 2018; 14:388-93.
24. Davies RL, Grosse VA, Kucherlapati R, Bothwell M. Genetic analysis of epidermal growth factor action: assignment of human epidermal growth factor receptor gene to chromosome 7. Proc Natl Acad Sci. 1980; 77:4188-4192.
25. Scaitriti M., Baselga J. The epidermal growth factor receptor pathway. A model for targeted therapy. Clin Cancer Res 2006; 12:5268-72.
26. M. J. Wieduwilt, M. M. Moasser. Cell mol life Sci 2008;65:1566-1584
27. Roskoski R., Jr The ErbB/HER receptor protein - tyrosine kinases and cancer. Biochem Biophys Res Commun. 2004; 319:1-11. Doi: 10.1016/j.bbrc.2004.04.150.
28. Poppleton HM, Wiepz GJ, Bertics PJ, Patel TB. Modulation of the protein tyrosine kinase activity and autophosphorylation of the epidermal growth factor receptor by its juxtamembrane receptor. Arch Biochem Biophys. 1999; 363:227-36.
29. Leemans CR, Braakhuis BJ, Brakehoff RH (2010). The molecular biology of head and neck cancer. Nat Rev 11:9-22.
30. Grandis JR, Tweardy DJ. Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. Cancer Res 1993; 53:3579-84.(27)
31. Maiti GP, Mondal P, Mukherjee N, Ghosh A, Ghosh S, Dey S, et al . Overexpression of EGFR in head and neck squamous cell carcinoma is associated with inactivation of SH3G12 and CDC25A genes. PLoS One 2013; 8:63440.
32. Rubin Grandis J, Twaerdy DJ, Mehem MF, Asynchronous modulation of transforming growth factor alpha and epidermal growth factor receptor protein expression in progression of premalignant lesions to head and neck squamous cell carcinoma. Clin Cancer Res 1998; 4:13-20.
33. Shin DM, Ro JY, Hong WK, Hittelman WN. Dysregulation of epidermal growth factor receptor expression in premalignant lesions during head and neck tumorigenesis. Cancer Res 1994; 54:3153-9.
34. Sakai H, Kawano K, Hishimoto N: immunohistochecmical localization of c-myc oncogene product and EGF receptor in oral squamous cell carcinoma. J Oral Pathol Med 1990, 19:1-4.
35. Vajaria BN, Patel KR, Begum R, Patel JB, Shah FD Patel PS. Signifance of phosphorylated epidermal growth factor receptor, matrix metalloproteinases, and E-cadherin in oral cancer. Tumor Microenviron 2018; 1:16-24.
36. Wilding J, Vousden KH, Soutter WP, McCrea PD, Del Buono R, Hgnatelli M. E-cadherin transfection down-regulates the epidermal growth factor receptor and reverses the invasive phenotype of human papilloma virus-transfected keratinocytes. Cancer Res 1996; 56:5285-92.
37. Zhou J, Tao D, Xu Q, Gao Z, Tang D. Expression of E-cadherin and Vimentin in oral squamous cell carcinoma. Int J Clin Exp Pathol 2015; 8:3150-4.
38. Aquino G, Pallone G, Santoro A, Liguori G, Franco R, { photo no.(36)}

39. Carpenter G. Receptors for epidermal growth factor and other polypeptide mitogens. Annu Rev Biochem. 1987; 56:881-914.
40. Zeineldin R, Hudson LG. Epithelial cell migration in response to epidermal growth factor. Methods Mol Biol. 2006; 327:147-158.
41. Rajaram P, Chandra P, Ticku S, Pallavi B K, Rudresh K B, Mansabdar P. Epidermal growth factor receptor. Role in human cancer. Indian J Dent Res 2017; 28:687-94.
42. Lee et al: Epidermal growth factor receptor regulates Beta catenin location, stability, and transcriptional activity in oral cancer. Molecular Cancer 2010 9:64.
43. Zuo JH, Zhu W, LiXH, YiH, Zeng GQ, *et al.* Activation of EGFR promotes squampous cell carcinoma SCC10A cell migration and invasion via inducing EMT-like phenotype change and MMP-9 mediated degradation of E-cadherin. J Cell Biochem 2011; 112:2508-17.
44. Burris HA, 3rd Overcoming acquired resistance to anticancer therapy:focus on the PI3K/AKT/mTOR pathway. Cancer Chemother Pharmacol. 2013; 4:829-842.
45. Gonzalez-Angulo AM, Ferrer- Lozano J, Stemke- Hale K, Sahin A, Liu S, Barrera JA, Burgues O, Lluch AM, Chen H, Hortobagyi GN, Mills GB, Meric Bernstam F. PI3K pathway mutations and PTEN levels primary and metastatic breast cancer. Mol Cancer Ther. 2011; 6:1093-1101.
46. Moscatello DK, Holgado-Madruga M, Emlet DR, Montomery RB, Wong AJ. Constitutive activation of phosphatidylinositol 3-kinase by a naturally occurring mutant epidermal growth factor receptor. J Biol Chem 1998;1:200-206.
47. Cai Y, Dodhia S, Su GH. Dysregulation in the PI3K pathway and targeted therapies for head and neck squamous cell carcinoma. Oncotarget 2017;8:22203-22217.
48. Ping Wee, Zhixiang Wang. Epidermal growth factor receptor cell proliferation
49. Hsu JY, Chang JY, Chang KY, Chang WC, Chen BK. Epidermal growth factor-induced pyruvate dehydrogenase kinase expression enhances head and neck squamous cell carcinoma metastasis via up-regulation of fibronectin. FASEB J 2017 Oct; 31(10): 4265-4276.
50. Zhimin LU, Guoqiang Jiang, Peter Blume- Jensen, and Tony Hunter. Epidermal growth factor-induced tumor cell invasion and metastasis initiated by dephosphorylation and downregulation of focal adhesion kinase. Molecular and Cellular Biology, June 2001, p.4016-4031.
51. Huang SH and O'Sullivan B: Oral cancer. Current role of Radiotherapy and Chemotherapy. Med Oral Pathol Oral Cir Bucal.18(2):e233-240,2013.
52. Shin DM, Donato NJ, Perez-SolerR, Shin HJ, Wu JY, Zhang P, Lawhorn K, Khuri FR, Glisson BS, Myers J, Clayman G, Pfister D, Falcey J, Waksal H Mendelsohn J and Hong Kong WK: Epidermal growth factor receptor targeted therapy with C225 and cisplatin in patients with head and neck cancer. Clin Cancer Res 7(5): 1204-1213, 2001.
53. Flavia Andressa Pidone Riberio, Juliana Noguti, Celina Tizuko Fujiyama Oshima and Daniel Araki Riberio. Effective Targeting of Epidermal Growth Factor Receptor (EGFR) for Treating Oral Cancer: A Promising Approach. Anticancer Research 34:1547-1552, 2014.
54. Galizia G, Lieto E, De Vita F, Orditura M, Castellano P, Troiani T, et al. Cetuximab, a chimeric human mouse anti-epidermal growth factor receptor monoclonal antibody, in the treatment of human colorectal cancer. Oncogene 2007; 26:3654-60.
55. Soulieres D, Senzer, NN,Vokes EE, Hidalg M, Agarawala SS, Siu LL. Multicenter phase II study of erlotinib and oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of head and neck. J Clin Oncol 22:77-85,24.

56. Choudhari, Sheetal Korde, Minal Chaudhary, Amol R. Gadbail, Aparna Sharma, and Satyajit Tekade. “Oxidative and Antioxidative Mechanisms in Oral Cancer and Precancer: A Review.” ORAL ONCOLOGY 50, no. 1 (January 2014): 10–18. https://doi.org/10.1016/j.oraloncology.2013.09.011.
57. Gadbail, A.R., S. Korde, M.S. Chaudhary, S.C. Sarode, S.M. Gondivkar, R. Dande, S.A. Tekade, M. Yuwanati, A. Hande, and S. Patil. “Ki67, CD105, and α-SMA Expression Supports Biological Distinctness of Oral Squamous Cell Carcinoma Arising in the Background of Oral Submucous Fibrosis.” Asian Pacific Journal of Cancer Prevention 21, no. 7 (2020): 2067–74. https://doi.org/10.31557/APJCP.2020.21.7.2067.
58. Kadashetti, Vidya, Minal Chaudhary, Swati Patil, Madhuri Gawande, K. M. Shivakumar, Snehal Patil, and R. C. Pramod. “Analysis of Various Risk Factors Affecting Potentially Malignant Disorders and Oral Cancer Patients of Central India.” JOURNAL OF CANCER RESEARCH AND THERAPEUTICS 11, no. 2 (June 2015): 280–86. https://doi.org/10.4103/0973-1482.151417.
59. Jaiswal, Shradha G., Amol R. Gadbail, Minal S. Chaudhary, Gagan R. Jaiswal, and Madhuri Gawande. “Correlation of Serum Levels of Vascular Endothelial Growth Factor with TNM Staging, Histopathologic Grading, and Surgical Therapy for Oral Squamous Cell Carcinoma.” QUINTESSENCE INTERNATIONAL 42, no. 9 (October 2011): 771–79.
60. Agarwal, A., N. Bhola, R. Kambala, and R.M. Borle. “Touch Imprint Cytology: Can It Serve as an Alternative to Frozen Section in Intraoperative Assessment of Cervical Metastasis in Oral Squamous Cell Carcinoma?” Journal of Oral and Maxillofacial Surgery 77, no. 5 (2019): 994–99. https://doi.org/10.1016/j.joms.2019.01.011.
61. Hande, Alka H., Deepali P. Mohite, Minal S. Chaudhary, Mimansha Patel, Priyanka Agarwal, and Shruti Bohra. “Evidence Based Demonstration of the Concept of `field Cancerization’ by P53 Expression in Mirror Image Biopsies of Patients with Oral Squamous Cell Carcinoma - an Immunohistochemical Study.” ROMANIAN JOURNAL OF MORPHOLOGY AND EMBRYOLOGY 56, no. 3 (2015): 1027–33.
62. Jagtap, Miheer Milind, Samarth Shukla, Sourya Acharya, Ankita Tamhane, and Arvind Bhake. “Utility of Histochemical and Immunohistochemical Profile in Grading of Squamous Cell Carcinoma of the Oral Cavity.” JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH 14, no. 1 (January 2020): EC1–5. https://doi.org/10.7860/JCDR/2020/42221.13396.