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

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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.

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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.

Conclusions:

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.

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