Short Communication

EGFR Isoforms Might be Responsible for the Diminished Treatment Outcome of EGFR Inhibitors

Journal of Pharmacology and Pharmacotherapeutics
17(1) 145–147, 2026

DOI: 10.1177/0976500X251321892
journals.sagepub.com/home/pha
Sage

Rajdeep Chakraborty[1,2], Pallavi Khodlan[1], Arthur Chien[3], Chao Shen[3], Thiri Zaw[4], Matthew Fitzhenry[4], Ardeshir Amirkhani[4] and Fei Liu[2]

Abstract

Epidermal growth factor receptor (EGFR) plays an active role during the progression of oral squamous cell carcinoma (OSCC). OSCC is the most common head and neck cancer. Cetuximab, which is an inhibitor of EGFR, was approved by the Food and Drug Administration (FDA) in 2006 for the treatment of head and neck cancer. After initial clinical success, Cetuximab proved to be ineffective in the management of aggressive or metastatic oral cancer lesions. We hypothesize that EGFR has multiple isoforms that lead to the failure of Cetuximab. A future study of EGFR isoforms and protein-interacting partners will address the issue.

Keywords

Anti-tumor reactivity, Cetuximab, epidermal growth factor receptor, oral cancer

Received 16 March 2024; **accepted** 31 January 2025

Introduction

Epidermal growth factor receptor (EGFR) is an established signaling pathway in cancer progression that cross-talks with nearly all proliferation and apoptotic mechanism-related proteins.[1] EGFR plays a pivotal role in oral squamous cell carcinoma (OSCC), affecting all the hallmarks of cancer. Additionally, in OSCC, EGFR is proposed to participate significantly in the prognosis of the disease.[2] EGFR is associated with aggressive behavior and poorer outcomes.[2] Cetuximab, an EGFR inhibitor, was approved by the Food and Drug Administration (FDA) in 2006 for the treatment of head and neck cancer. Thereafter, in 2009, FDA approved Cetuximab in combination with platinum-based chemotherapy with 5-fluorouracil for the treatment of recurrent, locoregional, or metastatic head and neck cancer, based on the clinical outcome of the EXTREME (ErbituX in first-line Treatment of REcurrent or MEtastatic head and neck cancer) trial.[3] Five-year survival data from phase 3 randomized trial and the relationship between Cetuximab-induced untoward clinical outcomes and overall survival data, which were stratified by pretreatment characteristics of radiation plus Cetuximab for locoregionally advanced head and neck squamous cell carcinoma, suggested no advantage in patients with age more than 65 years.[4] Cetuximab proved to be beneficial only for patients with primary oropharyngeal lesions or when Cetuximab is administered in altered fractionation with a concomitant boost of radiation therapy.[4] Cetuximab could not produce an appreciable treatment outcome in human papillomavirus-positive (HPV-positive) OSCC patients.[4] *In vitro* studies were concordant with the clinical output, where Cetuximab failed to induce radiosensitivity in HPV-positive head and neck squamous cell carcinoma cell lines. Furthermore, Cetuximab and nivolumab (immune checkpoint inhibitor, PD-1 inhibitor) treated patients with recurrent and metastatic head and neck squamous cell carcinoma were predicted to fail based on early treatment response dynamics.[5] ARTSCAN III (randomized phase III

[1]Applied Biosciences, Faculty of Science and Engineering, Macquarie University, Sydney, NSW, Australia
[2]School of Natural Sciences, Faculty of Science and Engineering, Macquarie University, Sydney, NSW, Australia
[3]Macquarie Analytical & Fabrication Facility, Faculty of Science and Engineering, Macquarie University, Sydney, NSW, Australia
[4]Australian Proteome Analysis Facility, Faculty of Science and Engineering, Macquarie University, Sydney, NSW, Australia

Corresponding author:
Rajdeep Chakraborty, Applied Biosciences, Faculty of Science and Engineering, Macquarie University, Sydney, NSW 2109, Australia; School of Natural Sciences, Faculty of Science and Engineering, Macquarie University, Sydney, NSW 2109, Australia.
E-mail: rajdeep.chakraborty@mq.edu.au

study comparing chemoradiotherapy with cisplatin compared to Cetuximab) found that cisplatin is better than Cetuximab in locoregionally advanced head and neck squamous cell carcinoma.[6] The possible reason for such a decline in the activity of the EGFR inhibitor is the presence of multiple isoforms of EGFR.[7] Post-translational modifications and protein interactions directly affect EGFR signaling and trafficking.[7] It has been recently reported that post-translational modifications generate various isoforms of the native peptide.[8] The variations in phosphorylation types for post-translational modifications result in the alteration of the functionality of EGFR.[9] Post-translational modifications also affect protein–protein interactions (PPIs). PPIs also affect the functionality of EGFR and the ability of Cetuximab to inhibit EGFR.[9] EGFR was previously found to participate in inhibiting the anti-tumor reactivity of immune cells. Recently, EGFR has been found to be interacting with signal transducer and activator of transcription 3 (STAT3), heterogeneous nuclear ribonucleoprotein M (HNRNPM), and plakophilin 3 (PKP3) in OSCC cells.[10] Interestingly, all these proteins participate in immune suppression in the tumor microenvironment.[10] Thus, EGFR participating in immunosuppression and variations in structure and function due to different sites of post-translational modification result in the lowering of treatment outcome of Cetuximab in aggressive OSCC. To substantiate the hypothesis, PPI networks should be studied in different oral cancer cell lines. Immunocytochemistry and immunohistochemistry should be performed using cell cultures and patient samples to determine the colocalization of EGFR and other immunomodulatory markers. The protein-binding partners of EGFR at different stages of disease proregression will eventually lead to the elucidation of the role of EGFR-interacting protein inhibition of anti-tumor reactivity of immune cells. Additionally, a transcriptomics assay to determine EGFR isoforms during the progression of oral cancer should be done. Finally, EGFR and its ligand 3D modeling should be done to predict the small molecules that are useful for the augmentation of the anti-cancer effect of Cetuximab. Overall, addressing the challenge of Cetuximab in managing the progression of oral cancer necessitates comprehensive molecular characterization of EGFR-interacting proteins and binding ligands. The molecular characterization will eventually lead to the development of newer pharmacological targets that can either minimize the use of Cetuximab or show a synergistic effect when administered along with Cetuximab.

Abbreviations

APAF: Australian Proteome Analysis Facility; **ARTSCAN:** A Randomized Phase III Study Comparing Chemoradiotherapy With Cisplatin Versus Cetuximab in Patients With Locoregionally Advanced Head and Neck Squamous Cell Cancer; **EGFR:** Epidermal growth factor receptor; **EXTREME:** ErbituX in first-line Treatment of REcurrent or MEtastatic head and neck cancer; **FDA:** Food and Drug Administration; **HNRNPM:** Heterogeneous nuclear ribonucleoprotein M; **HPV:** Human papillomavirus; **OSCC:** Oral squamous cell carcinoma; **PD-1:** Programmed death-1; **PKP3:** Plakophilin 3; **PPIs:** Protein–protein interactions; **PTM:** Post-translational modification; **STAT3:** Signal transducer and activator of transcription 3.

Acknowledgments

The authors would like to thank Dr. Fiona Simpson, University of Queensland, Frazer Institute and Dr. Charbel Darido, Peter MacCallum Cancer Centre, University of Melbourne, for providing valuable suggestions regarding head and neck cancer and EGFR. The authors gratefully acknowledge the Australian Proteome Analysis Facility (APAF), Macquarie University, and the microscopy unit of Macquarie Analytical & Fabrication Facility for their valuable suggestions during this work.

Author Contribution

Conceptualization, R.C.; literature search and writing—original draft preparation, R.C. and P.K.; writing—review, all authors; supervision, A.C., C.S., T.Z., M.F., A.A., and F.L.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Statement and Informed Consent

The work did not require any use of cell line or lab work, so no biosafety approval required. The work did not require use of patient samples, so no human ethics approval or informed consent required.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Rajdeep Chakraborty https://orcid.org/0000-0001-8210-0459

References

1. Nelhűbel GA, Cserepes M, Szabó B, et al. EGFR alterations influence the cetuximab treatment response and c-MET tyrosine-kinase inhibitor sensitivity in experimental head and neck squamous cell carcinomas. *Pathol Oncol Res*. 2021; 27: 620256.
2. Ribeiro FA, Noguti J, Oshima CT, Ribeiro DA. Effective targeting of the epidermal growth factor receptor (EGFR) for treating oral cancer: a promising approach. *Anticancer Res*. 2014; 34(4): 1547–1552.
3. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008; 359(11): 1116–1127.
4. Krishnamurthy S, Ahmed I, Bhise R, et al. The dogma of cetuximab and radiotherapy in head and neck cancer—a dawn to dusk journey. *Clin Transl Radiat Oncol*. 2022; 34: 75–81.
5. Glazar DJ, Johnson M, Farinhas J, et al. Early response dynamics predict treatment failure in patients with recurrent and/or

metastatic head and neck squamous cell carcinoma treated with cetuximab and nivolumab. *Oral Oncol*. 2022; 127: 105787.
6. Gebre-Medhin M, Brun E, Engström P, et al. ARTSCAN III: A Randomized Phase III Study Comparing Chemoradiotherapy With Cisplatin Versus Cetuximab in Patients With Locoregionally Advanced Head and Neck Squamous Cell Cancer. *J Clin Oncol*. 2021; 39(1): 38–47.
7. Negrón-Vega L, Cora EM, Pérez-Torres M, Tang SC, Maihle NJ, Ryu JS. Expression of EGFR isoform D is regulated by HER receptor activators in breast cancer cells. *Biochem Biophys Rep*. 2022; 31: 101326.
8. Hermann J, Schurgers L, and Jankowski V. Identification and characterization of post-translational modifications: clinical implications. *Mol Aspects Med*. 2022; 86: 101066.
9. Malik A, Afaq S, Alwabli AS, Al-Ghmady K. Networking of predicted post-translational modification (PTM) sites in human EGFR. *Bioinformation*. 2019; 15(7): 448–456.
10. Chakraborty R, Darido C, Tay A, et al. Inhibition of anti-tumour reactivity of immune cells in the salivary gland cancer: a proteomic approach. *Oral Oncol Rep*. 2024; 100160(9): 1–9.