Amplification of EGFR Mutations, vIII and vIVa, in Two Patients with Esophageal Squamous Cell Carcinoma, hints at Common Binding Targets

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Abstract

A recent study identified two EGFR gene mutations commonly found in the EGFR gene for glioblastoma multiforme (GBM), EGFRvIII, and EGFRvIVa in two of ten African American patients with esophageal squamous cell carcinoma (ESCC). EGFRvIII mutation is a key driver in tumor progression and is associated with a poor prognosis as it lacks the L1 and CR1 domains, which are crucial for ligand binding. Herein a discussion is presented on the identification of these rare and clinically significant mutations in ESCC patients, which raises important questions about the functional implications of these mutations, the feasibility of observational clinical trials, and the use of off-label EGFR inhibitors.

Keywords:
EGFR, Esophageal Squamous Cell Carcinoma, Glioblastoma Multiforme, Genomics, Targeted Therapy

Introduction

Esophageal cancer has a strikingly low survival rate, mainly due to the lack of diagnostic markers for early detection and effective therapies. Their incidence rate in the U.S. alone still remains skewed in the disfavor of the African American population. According to recent trends from the NCI SEER data, the incidence rates of individuals in African Americans (AA) diagnosed with esophageal squamous cell carcinoma (ESCC) are nearly twice as much as combined rates from all other races (Fig 1). Though the incidence rates have witnessed a remarkable decline in the AA population and their predisposition to ESCC, the resulting mortality rates still remain high compared to the rest of the population in the US.

Recently, a study by whole-genome sequencing was carried out in matched tumor and normal tissues from 10 African American patients to identify tumor-specific genomic abnormalities. Two interesting mutations were identified in the EGFR gene that is typically found in the EGFR gene for Glioblastoma Multiforme (GBM), EGFRvIII, and EGFRvIVa. These findings raise important questions about the functional implications of these mutations between these two cancers, the feasibility of observational clinical trials, and the use of off-label EGFR inhibitors; a discussion of which is presented below.
Figure 1: Incidence rates of Esophageal Squamous Cell Carcinoma across different races over the years (NCI SEER Data). Despite a remarkable decrease in the incidence rates over the years the African American population still shows twice as much combined average rates of all other races.

Discussion

Functional roles

EGFR plays an essential role in the nervous system in various ways, including 1) Maintenance of the neural stem cells pool, 2) Maturation and functions of astrocytes, 3) Oligodendrogenesis, and 4) neurite outgrowth in the CNS. They also play a role in PNS development. As a result, alterations in EGFR, like GBM, possibly have their causes rooted in the appropriate mutations. In lung cancers, the ramifications of mutations in kinase domains get expressed differently to their interactions and cross-talk with other signaling components in the milieu. For example, there is a substantial cross-talk and interplay between other tyrosine kinase mediators like Vascular Endothelial Growth Factor (VEGF) and Interferon-Gamma (IFNg).

Compared to the EGFR gene, the EGFRvIII variant has missing L1 and CR1 domains due to the deletion of exons 2-7 (Fig 2). This truncation results in the inability of the receptor to bind to any ligand, thus becoming an important driver in tumor progression and a marker of poor prognosis. There are two variations of EGFR vIV, namely EGFR-vIVa and EGFR-vIVb, which contain deletions of exons 25-27 and 25-26, respectively. Thus, EGFRvIII and EGFRvIVA/b are both mutants of the epidermal growth factor receptor (EGFR), but they differ in the parts of the receptor that they lack. EGFRvIII lacks a portion of the ligand-binding cleft, while EGFRvIVA/b lacks internal segments distal to the intracellular tyrosine kinase domain.
Implications of common mutations in a gene between specific cancers

The predominance of domain-specific mutations for a given gene in different cancers is mainly a manifestation of the functions driven by those domains, the upstream and downstream signaling processes, and ligand interactions that are intertwined with such domains. When a similar pattern of mutations for a gene gets reflected in another form of cancer like ESCC but not in yet other forms of cancers e.g., lung cancers, then there is a possibility of similar interacting ligands or signaling interactions in EGFR. This opens up the need to look into the basic binding mechanisms of EGFR and its interactions. Questions arise as to what is common in this gene function in these two tissues.

There have been very few studies on the presence and distribution of EGFR mutations and their relevance in the process of oncogenesis in ESCC. Their presence is rare and insignificant 8 OR their significance has been less studied. Either way, their copy number is directly related to poor prognosis 9 and changes associated with them, including copy number OR mutations, are one of the changes associated with the development of ESCC 10.

Keeping these in the backdrop, we propose that the interacting partners unique to the mutation-specific domains of the EGFR gene in Glioblastoma might match up in functional aspects with those involved in Esophageal Squamous Cell Carcinoma. It is worth looking into the interacting partners of the EGFR-vIII domain in these two cancers. For example, the OSMR gene (Oncostatin M Receptor beta) is a critical regulator of glioblastoma tumor growth that orchestrates a feed-forward signaling mechanism with EGFRvIII 11. Interestingly, an RT-PCR detected overexpression of the alternatively spliced OSMR β transcript in 9 of 11 ESCCs 12. Are these phenomena concomitant in these two cancers? How many other interacting partners of
EGFR in vIII and vIV exist that are affected in these cancers? Addressing these can provide greater insights into the role of these genes in the signaling network.

### Need for a larger cohort to study these mutations in ESCC

Further investigations in a larger cohort of patient samples are needed to confirm this link and to better understand the role of EGFR mutations in ESCC tumorigenesis in AA patients. This research could lead to the development of targeted therapies that are specifically tailored to AA patients with ESCC.

Here are some specific areas of research that could be explored:

- The frequency of EGFR mutations in AA patients with ESCC compared to other racial groups.
- The types of EGFR mutations that are most common in AA patients with ESCC.
- The impact of EGFR mutations on the prognosis of ESCC in AA patients.
- The development of targeted therapies that are effective against EGFR-mutant ESCC in AA patients.

Investigating these aspects could lead to improved outcomes for AA patients with ESCC. Targeted therapies that are specifically tailored to AA patients could provide a more effective treatment option and could help to reduce the high mortality rates of this disease in the AA population.

### Common mutations, domains, and off-label approaches

The EGFRvIII mutation lacks the L1 and CR1 domains, which are critical for ligand binding, so it becomes a key driver in tumor progression and is linked to poor prognosis 13. Therefore, exploring potential shared targets between GBM and ESCC with this mutation profile could lead to the development of effective therapies. A few approaches have emerged in the last few years that specifically target the vIII variants in EGFR 14 15. For example, Rindopepimut showed promising results in a phase-II multicenter trial with improved progression-free survival and overall survival metrics 16. These could carry potential use as an off-label treatment for ESCC with EGFRvIII amplification. Alternatively, developing novel therapies that target EGFRvIII or its downstream signaling pathways could be considered for ESCC patients with this mutation profile. Further research and clinical trials are needed to validate these approaches, but they hold promise to improve outcomes for patients with ESCC and EGFRvIII amplification.

### References


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