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Elucidating the mechanisms of resistance to tyrosine kinase inhibitors in lung cancer patients

Asim Joshi[1,3], Anuradha Chougule[2], Pratik Chandrani[1,3], Vaishakhi Trivedi[2], Prajish Iyer[1,3], Kumar Prabhash[2] and Amit Dutt[1,3#]

[1]Integrated Genomics Laboratory, Advanced Centre for Treatment Research Education In Cancer (ACTREC), Tata Memorial Centre, Navi Mumbai, Maharashtra 410210, INDIA

[2]Department of Medical Oncology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, INDIA

[3]Homi Bhabha National Institute, Training School Complex, Anushakti Nagar, Mumbai 400094, INDIA

[*]Corresponding author: adutt@actrec.gov.in

Abstract

Introduction: Lung tumors with mutations in epidermal growth factor receptor (*EGFR*) gene represent a clinically distinct subtype of lung cancer and are observed at a frequency of 23% among Indian patients. The standard practice for treatment of *EGFR* mutated lung cancer patients includes tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib. Although initial clinical responses are observed, resistance to TKIs develops within year from the start of treatment. In about fifty percent of cases, the resistance is caused due to a secondary T790M mutation in the *EGFR* gene. Additionally, MET amplification and histological transformation of tumors are known to confer TKI resistance in a small subset of patients. Nonetheless, there is an unmet need to elucidate novel ways by which lung tumors acquire resistance to EGFR targeting TKIs.

Objectives: To delineate novel mechanisms of acquired resistance to EGFR-TKIs by characterizing the differential profile of drug sensitive and resistant state among lung tumors using integrated genomics approaches.

Material and Methods: A retrospective collection of FFPE DNA samples (n=45) from tumors at baseline and rebiopsy along with paired blood sample was done for a total of 15 *EGFR* mutated lung cancer patients. Only tumor samples which were negative for EGFR T790M (as confirmed by orthologous technologies) were selected in the study with anticipation that such samples would be enriched novel resistance mechanisms. Whole exome sequencing at an average coverage of 100X was performed for these samples.

Results: The whole exome data was analyzed using an in-house developed pipeline. Of all the known resistance mutations, we identified *EGFR* T790M mutation in five out of fifteen patients. Other than T790M we expect to identify novel resistance causing mutations from the analysis of ten patients with unknown resistance mechanisms. Functional validation of this resistance specific alterations would be performed *in vitro* using drug sensitive lung cancer cell lines.

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