Abstract

Epidermal growth factor receptor inhibitors (EGFRi) have exhibited promising clinical outcomes in the treatment of various cancers; however, their widespread application has been limited by low patient eligibility and the emergence of resistance. To address these challenges, we conducted an integrative analysis of multi-omics and phenotypic data derived from more than 1000 cancer cell lines. We explored molecular signatures linked to EGFRi responsiveness and found that expression signatures involved in the estrogen response could recapitulate cancer cell dependency on EGFR, a phenomenon not solely attributable to EGFR-activating mutations. By correlating genome-wide loss-of-function screening data with EGFRi responses, we identified chemokine receptor 6 (CCR6) as a potential druggable target to mitigate EGFRi resistance. To verify this prediction, we employed two sets of isogenic cell models and demonstrated that the pharmacological inhibition of CCR6 effectively reversed acquired EGFRi resistance. Subsequent investigation of the transcriptome profile following CCR6 inhibitor treatment revealed a disruption to mitochondrial oxidative phosphorylation, a cellular process commonly associated with therapy resistance. Our data-driven approach highlights the significance of integrative omics analysis in identifying novel drug-response biomarkers and therapeutic targets for resistance, thus expanding their applicability to a broader range of patients and enhancing the effectiveness of targeted therapies.