# Accepted Manuscript


mTORC2 contributes to the metabolic reprogramming in EGFR tyrosine-kinase inhibitor resistant cells in non-small cell lung cancer

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PII: S0304-3835(18)30483-X

DOI: 10.1016/j.canlet.2018.07.025

Reference: CAN 13999

To appear in: *Cancer Letters*

Received Date: 8 May 2018

Revised Date: 17 July 2018

Accepted Date: 17 July 2018

Please cite this article as: C.-T. Chiang, A.N. Demetriou, N. Ung, N. Choudhury, K. Ghaffarian, D.L. Ruderman, S.M. Mumenthaler, mTORC2 contributes to the metabolic reprogramming in EGFR tyrosine-kinase inhibitor resistant cells in non-small cell lung cancer, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.07.025.

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**Abstract**

Non-small cell lung cancer (NSCLC) patients with activating *EGFR* mutations are often successfully treated with EGFR tyrosine kinase inhibitor (TKI) such as erlotinib; however, treatment resistance inevitably occurs. Given tumor metabolism of glucose and therapeutic response are intimately linked, we explored the metabolic differences between isogenic erlotinib-sensitive and -resistant NSCLC cell lines. We discovered that the growth of erlotinib-resistant cells is more sensitive to glucose deprivation. Seahorse metabolic assay revealed erlotinib-resistant cells have lower spare respiratory capacity (SRC), an indicator of metabolic flexibility, compared to erlotinib-sensitive cells. Additionally, we found downstream components of mTORC2 signaling to be phosphorylated in erlotinib-resistant cells. Knockdown of an mTORC2 component, Rictor, enhanced the SRC and rescued the growth rate of erlotinib-resistant cells during glucose deprivation. Among NSCLCs with activating *EGFR* mutations, gene sets involved in glucose metabolism were enriched in patients with high expression of p-NDGR1, a readout of mTORC2 activity. Furthermore, overall survival was negatively correlated with p-NDRG1. Our work uncovers a link between mTORC2 and metabolic reprogramming in EGFR TKI-resistant cells and highlights the significance of mTORC2 in the progression of *EGFR*-mutated NSCLC.

**Key Words:**

NSCLC, EGFR TKI resistance, glucose metabolism, mTORC2