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MERTK promotes resistance to irreversible EGFR TKIs in NSCLCs expressing wild-type EGFR

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Lung cancer is the leading cause of cancer-related death with poor survival rates worldwide. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers and 60% of these have wild-type EGFR (wtEGFR) overexpression, which portends a poor prognosis. However, agents targeting EGFR have limited utility in preclinical models with wtEGFR overexpression. Our laboratory previously identified MERTK receptor tyrosine kinase as a potential therapeutic target in NSCLC and developed MRX-2843, a novel MERTK-selective small molecule inhibitor with favorable properties for clinical translation. MRX-2843 mediated potent anti-tumor effects in the wtEGFR-expressing A549 NSCLC line *in vitro* and *in vivo*. In addition, we screened a library of 378 kinase inhibitors in various development stages and identified favorable interactions between MRX-2843 and multiple irreversible EGFR TKIs, including CO-1686 and Osimertinib/AZD-9291. Synergistic inhibition of cell expansion was observed in a spectrum of wtEGFR-expressing NSCLC cell lines. Further, we found that wtEGFR and MERTK were frequently co-expressed and co-immunoprecipitated from NSCLC cell lysates. Mechanistically, combined treatment with CO-1686 and MRX-2843 inhibited MERTK and EGFR phosphorylation and downstream PI3K-AKT and MAPK-ERK signaling. In contrast, MERTK, EGFR, and downstream signaling were not efficiently inhibited in response to treatment with single agents. Furthermore, tumor size was reduced in response to treatment with combination therapy relative to single agent treatments in a wtEGFR-expressing xenograft model. Taken together, our data provide rationale for combined treatment with MRX-2843 and an irreversible EGFR inhibitor as a novel strategy for treatment of NSCLC with wtEGFR overexpression.

Biography

Dan Yan received her MD and PhD degrees from Tongji Medical College in China. She has published 22 research papers in journals including Science *Translational Medicine, Proceedings of the National Academy of Sciences (PNAS), and Journal of Biochemistry*. She has reviewed multiple journals and is an Editorial Board Member for Results in *Immunology and Gavin Journal of Blood*. She joined the Emory Faculty in 2015 as a newly appointed Instructor focusing on characterization of roles for MERTK in non-small cell lung cancer (NSCLC) with an emphasis on identification of other pathways that cooperate with MERTK to promote tumorigenesis.

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