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Commentary: New players in epidermal growth factor receptor tyrosine kinase inhibitor resistance

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CENTRAL MESSAGE

Resistance to EGFR tyrosine kinase inhibitors is complex and will require multidisciplinary teams to develop effective treatment regimens.

Targeted inhibition of the epidermal growth factor receptor (EGFR) tyrosine kinase in lung adenocarcinoma is limited by acquired resistance. Better understanding of the development of this resistance is a significant unmet need in lung adenocarcinoma treatment. The group at Medical University of South Carolina in the present study¹ has identified a mechanism for resistance in EGFR mutant lung adenocarcinoma that relies on the NRP2B-GSK3B-PTEN-AKT axis. This group has previously demonstrated that NRP2B is absent from normal lung tissue and upregulated in lung cancer and that its presence correlates with poor clinical outcomes.² The present study builds on the previous work. First, shRNA inhibition of NRP2B led to 100-fold decrease in persister cells after gefitinib treatment. In addition, NRP2B knockdown can sensitize some EGFR wild-type cells to gefitinib. In HEK293 cells, expression of NRP2B leads to greater phosphorylation of phosphatase and tensin homolog (PTEN) and its subsequent post-translational degradation. NRP2B binds glycogen synthase kinase 3 beta (GSK3 β) preferentially with subsequent GSK3 β -dependent phosphorylation of PTEN. Migration and development of persister cells are dependent on GSK3 β signaling. Importantly for therapeutic development, lack of NRP2B is well tolerated by cells. These are important findings that will help the EGFR resistance field to move forward.

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The field of tyrosine kinase inhibitor (TKI) resistance is very complex. Although EGFR inhibition has represented a great advance in lung cancer therapy, acquired resistance has limited its effectiveness in improving long-term survival rates. Many mechanisms of resistance have been described. Most commonly, the development of T790M mutation renders the EGFR protein resistant to first- and second-generation TKIs (gefitinib, erlotinib, icotinib, afatinib). Recently, the third-generation TKI osimertinib has been demonstrated to be effective in EGFR mutant lung adenocarcinoma even in the first-line setting.³ However, other resistance mechanisms representing alternative downstream signaling pathways are common even after osimertinib treatment and must be addressed. These include MET activation, phosphoinositide 3-kinase (PI3K) pathway activation, and KRAS activation, among others.⁴

One of the strengths of the current work is that some of these clinical issues are addressed. Osimertinib is used to address resistance to third-generation inhibitors. The mechanism proposed in the current article acts through PTEN/AKT, which are downstream effectors of PI3K. These careful, well-controlled signal transduction experiments are being performed by a multidisciplinary team of scientists and surgeon-scientists.

As the authors acknowledge, work such as this raises many new questions that must be addressed to achieve clinical relevance. These mechanisms must be validated using in vivo models. In terms of planning eventual treatment, the question of whether NR2B inhibition or downstream PI3K signaling should be targeted must be answered. For surgeons, whether EGFR inhibition or EGFR inhibition in

tandem with resistance inhibitors is appropriate in an adjuvant setting or in an induction setting will be important issues to address. The National Cancer Institute's ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) trial only uses the first-generation TKI erlotinib in EGFR-mutant patients. Finally, at present, immunotherapy approaches are not effective in patients with EGFR mutations. Whether programmed cell death protein 1/programmed death-ligand 1 expression and tumor mutational burden are increased when NR2B is upregulated will be an interesting question.

In summary, this is a very interesting study that presents a novel resistance mechanism of EGFR TKI resistance. Elegant signal transduction experiments are described that may eventually lead to therapeutic

advances. Surgeons must be involved in and aware of this type of research so that we can develop new therapies for these patients and communicate effectively with oncologists and patients.

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Commentary: Keeping the target painted for precision cancer therapy

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Observations that activating mutations in the *epidermal growth factor receptor (EGFR)* gene confer sensitivity to EGFR-tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib ushered in the modern era of targeted therapy for non-small cell lung cancer (NSCLC).^{1,2} EGFR mutations occur in approximately 20% of NSCLC, typically in female patients, nonsmokers, and patients

CENTRAL MESSAGE

Acquired resistance to EGFR-TKI in NSCLC is associated with up-regulation of NRP2b. Targeting NRP2b may be a novel strategy to restore and maintain sensitivity to these agents for lung cancer therapy.

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with adenocarcinomas.³ Despite impressive initial responses, virtually all patients develop resistance to EGFR-TKI due to secondary mutations in *EGFR*, mutations that activate survival signaling pathways such as *MET*, evolution of a small cell lung cancer phenotype, or epithelial-to-mesenchymal transition (EMT).⁴ As such, delineation of mechanisms conferring resistance to EGFR-TKI is a major focus of investigative efforts in thoracic oncology.

In this issue of the *Journal*, Dimou and colleagues⁵ examined the role of *Neuropilin-2b (NRP2b)* in acquired resistance to EGFR-TKI in NSCLC. Previous studies by this