managing outcomes of patients undergoing targeted therapy and offer new avenues towards treatment of TKI resistant tumors. References:

The YAP/FOXM1 Axis Regulates EMT-Associated EGFR Tyrosine Kinase Inhibitor Resistance and Increased Expression of Spindle Assembly Checkpoint Components

M.B. Nilsson,1 H. Sun,1 J. Robichaux,1 L. Diao,2 Y. Xi,2 P. Tong,2 L. Sheng,2 M. Hofstad,1 M. Kawakami,1 X. Le,1 X. Liu,1 Y. Fang,1 A. Poteete,1 M. Vailati NEGRO,2 H. Tran,1 E. Dmitrovsky,1 D. Peng,1 D. Gibbons,1 J. Wang,1 J.V. Heymach,1 1Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX/US, 2Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX/US

While EGFR mutant NSCLC patients are initially responsive to EGFR targeted therapies, resistant disease inevitably emerges. In nearly half of resistance cases, tumors lack secondary EGFR mutations such as T790M and are refractory to 2nd- and 3rd-generation EGFR tyrosine kinase inhibitors (TKI). We and others have also observed that EGFR-independent resistant tumor cells may undergo a histologic and functional transformation through epithelial-to-mesenchymal transition (EMT) (Byers et al., 2013; Chung et al., 2011; Uramoto et al., 2010; Zhang et al., 2012), which can occur concurrently with other genomic alterations. The lack of treatment regimens with efficacy against EGFR-independent EGFR TKI resistance remains a major clinical challenge. We investigated transcriptomic and proteomic alterations that occur in NSCLC cells with acquired resistance to EGFR TKIs that occurs independent of EGFR and c-Met and screened >1,300 compounds to identify targetable vulnerabilities. T790M-negative EGFR TKI resistance was associated with evidence of a mesenchymal transition along with increased activation of the YAP/FOXM1 transcriptional program and a broad-spectrum multidrug resistance phenotype. EGFR TKI resistant cells displayed increased expression of spindle assembly checkpoint (SAC) proteins PLK1, Aurora kinases, survivin, and KSP, and expression of these proteins was dependent on the YAP/FOXM1 axis. Consistent with recent reports (Bertran-Alamillo et al., 2019; Shah et al., 2019), EGFR TKI resistant cells were found to be sensitive to aurora kinase inhibitors. We further determined that EGFR TKI resistant cells were likewise highly sensitive to inhibitors of components of the spindle assembly checkpoint (SAC) pathway including PLK1, KSP, and survivin, and treatment with these agents resulted in the accumulation of cells in the G2/M phase of the cell cycle and mitotic catastrophe. Using a patient-derived model of T790M negative EGFR TKI resistance, we observed that treatment with SAC component inhibitors, alisertib, ispinesib, or volasertib significantly inhibited tumor growth compared with vehicle-treated tumors. Analysis of NSCLC clinical data revealed that FOXM1 expression correlated with expression of SAC components including PLK1, Aurora kinases, KSP, and survivin. Moreover, in EGFR mutant NSCLC patients, high FOXM1 expression was associated with a worse clinical outcome compared to EGFR mutant NSCLC patients with low expression of FOXM1. In resistant models, targeting of YAP reduced FOXM1 expression and expression of SAC components. In conclusion, we provide novel insights into the molecular alterations associated with EGFR TKI resistance and demonstrate that upregulation of SAC components in EGFR TKI resistant cells occurs through the activation of the YAP/FOXM1 pathway. These results support the future targeting of these pathways in NSCLC patients with EGFR-independent resistance to EGFR-targeted agents.