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The rationale for dual targeting MET and EGFR in non-small cell lung cancer

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Abstract

Non-small cell lung cancer (NSCLC) accounts for 80% of lung cancer, which is the leading cause of death among all human cancers. Receptor tyrosine kinases (RTKs) play important roles in NSCLC development and progression, and are attractive targets for cancer intervention. Both MET and EGFR are RTKs that are frequently activated in NSCLC either by overexpression, amplification or mutation. EGFR-targeted therapies (erlotinib and gefitinib) have been used for treating advanced lung cancer patients; however such treatments primarily benefit patients who carry sensitive EGFR mutations, leaving the majority of patients refractory to EGFR-targeted therapy. MET is often co-expressed with EGFR, and MET amplification is also one of the resistance mechanisms for escaping EGFR-targeted therapy. We reasoned that MET and EGFR cooperate in driving NSCLC development and progression, and MET inhibition would sensitize cancer cells lacking EGFR mutations to EGFR-targeted therapy. Using both in vitro cell-based assays and in vivo preclinical xenograft model systems, we demonstrated that combined inhibition of MET and EGFR significantly strengthened anti-cancer effects against NSCLC tumors in cellular context-dependent manners: enhancing suppression of proliferation with or without inducing apoptosis, and/or preventing a resistant mechanism that mutually bypasses individual inhibitor treatment. These data provide mechanistic understanding of how combination therapies targeting both MET and EGFR improves efficacy and reveal a potentially effective treatment regimen for NSCLC patients who lack EGFR mutations.

Biography

Yu-Wen Zhang, M.D., Ph.D., is a research assistant professor in the Center for Cancer and Cell Biology, Van Andel Research Institute. He received his M.D. from Fudan University Shanghai Medical College (formerly Shanghai Medical University), China in 1989, and his Ph.D. (Doctor of Medical Science) from Kyoto University, Japan in 1997. Dr. Zhang has published over 25 articles in peer-reviewed scientific journals and book chapters. His research focuses on understanding the role of receptor tyrosine kinases (RTKs) signaling, particularly MET and EGFR in cancer and other diseases, and exploring therapeutic strategies by targeting these RTK pathways for disease intervention.