Investigating Combinatorial Ligand Addiction Provides Insights into Rational Drug Combinations in Cancer Therapy

Emily A. Pace[1,2], Diana H. Chai, Anand Parikh, Ashish Kalra, Shinji Oyama, Bryan Johnson, Gege Tan, Raghida Bukhalid, Ulrik B. Nielsen[1], and Birgit Schoeberl[1]

***Short Abstract* — Cancer, the second most common cause of death in the U.S., is a collection of diseases caused by uncontrolled cell growth and metastasis. Targeted therapies, designed to specifically block cancer cell growth, are mainly effective in rare subsets of patients with tumors that are addicted to single oncogenes. Here, evidence is provided that targeted therapies are also effective in tumors that are dependent on multiple growth factors – a phenomenon called combinatorial ligand addiction. Combinatorial ligand addiction creates a new rationale for therapeutic combinations to improve efficacy and prevent resistance in cancer cells that are treated with current targeted drugs.**

***Keywords* — combinatorial ligand addiction, oncogene, autocrine signaling, EGFR, ErbB, ErbB3, MET, PI3 kinase, AKT, MAP kinase, ERK.**

I. Purpose

THE purpose of this work is to provide a network understanding of combinatorial ligand activation of the ErbB pathway. Dysregulation of the ErbB pathway has been implicated in many cancers[1,2]. Oncogenic activation of the pathway through ErbB receptor overexpression and activating mutations is the major rationale for development of current ErbB-targeted therapies[3,4,5] However, the role of combinatorial ligand addiction as a mechanism for driving tumor growth and progression, and its implication in insensitivity or resistance to current ErbB-targeted therapies has been greatly underappreciated. Many studies have characterized ErbB ligands as individual components; however, not much is known about autocrine signaling between ErbB ligands and receptors on a network level, which promote cell growth and survival by activating PI3 kinase and MAP kinase signaling cascades.

II. Results

In this study, we show that ErbB autocrine signaling is present across a broad set of tumor cells and may play an important role in driving both combinatorial ligand and oncogene-addicted tumors. Specifically, it is shown that ligands that bind the EGFR family and the hepatocyte growth factor receptor (HGFR/MET) can activate protein kinase B (PKB/AKT) across a broad set of cancer cell lines, suggesting that ligand signaling is redundant and widespread. Furthermore, it is shown that cell lines with and without known oncogene-addiction express autocrine ligands and have improved growth inhibition with drug combinations that include autocrine ligand-blocking antibodies.

A. ErbB and MET ligands activate PI3 kinase/AKT in many cancer types

B. Oncogene-addicted cells have distinct protein profiles

C. Co-inhibiting EGFR wild-type cell line with EGFR and ErbB3 ligand blocking antibodies better inhibits cell viability and signaling

D. Combinations with ligand-blocking antibodies synergistically inhibit oncogene-addicted cell lines

III. Conclusion

Traditional drug discovery methods focus on understanding one interaction at a time. However, in this study, we show how a systems approach to drug discovery can be applied to identify a previously unknown and complementary mechanism of inhibiting the ErbB receptor signaling network. We anticipate that similar approaches can be used to predict drug combinations for the effective treatment of patients with tumors that are oncogene-addicted, ligand-addicted, or both [6].

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[1] Merrimack Pharmaceuticals, Inc., One Kendall Square, Building 700, Cambridge, MA 02139, USA. E-mail: bschoeberl@merrimackpharma.com

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