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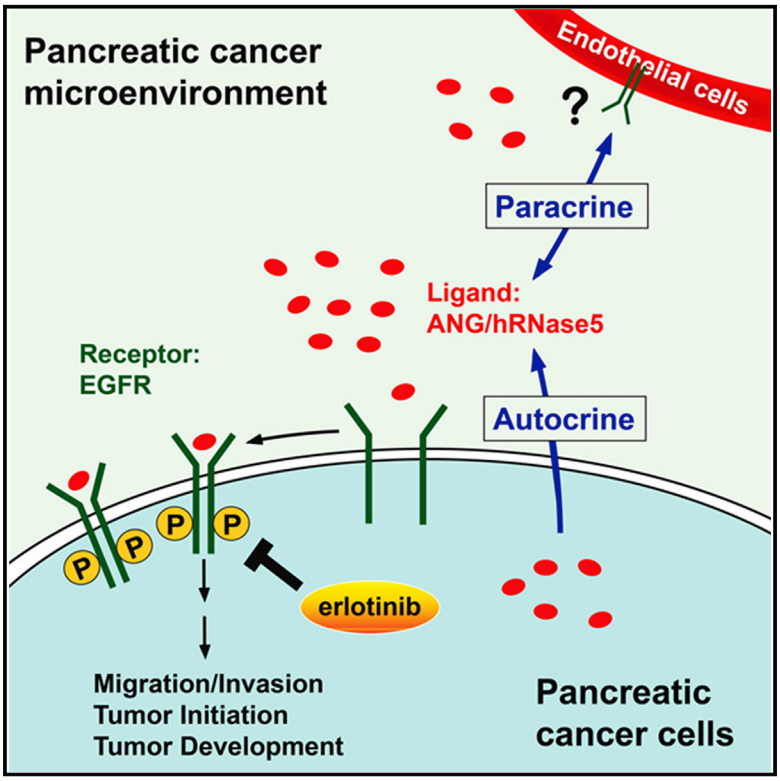
Angiogenin/Ribonuclease 5 Is an EGFR Ligand and a Serum Biomarker for Erlotinib Sensitivity in Pancreatic Cancer

Graphical Abstract



Highlights

- ANG acts as an EGFR ligand in an RNase catalytic-independent manner
- Depletion of ANG highlights an oncogenic role of the ANG-EGFR axis in PDAC
- High ANG level serves as a serum biomarker to predict erlotinib response
- New insight into ligand-receptor relationship between RTK and RNase families

Authors

Ying-Nai Wang, Heng-Huan Lee, Chao-Kai Chou, ..., Milind Javle, Anirban Maitra, Mien-Chie Hung

Correspondence

mhung@mdanderson.org

In Brief

Wang et al. identify angiogenin (ANG) as a ligand for epidermal growth factor receptor (EGFR). ANG-mediated EGFR activation can trigger oncogenic transformation, and high ANG in the plasma of pancreatic adenocarcinoma patients positively correlates with response to the EGFR inhibitor erlotinib.

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Angiogenin/Ribonuclease 5 Is an EGFR Ligand and a Serum Biomarker for Erlotinib Sensitivity in Pancreatic Cancer

Ying-Nai Wang,[1,8,10] Heng-Huan Lee,[1,10] Chao-Kai Chou,[1,8] Wen-Hao Yang,[1] Yongkun Wei,[1] Chun-Te Chen,[1] Jun Yao,[1] Jennifer L. Hsu,[1,8] Cihui Zhu,[1] Haoqiang Ying,[1,7] Yuanqing Ye,[2] Wei-Jan Wang,[1] Seung-Oe Lim,[1] Weiya Xia,[1] How-Wen Ko,[1] Xiuping Liu,[3] Chang-Gong Liu,[3] Xifeng Wu,[2,7] Huamin Wang,[4] Donghui Li,[5,7] Laura R. Prakash,[6] Matthew H. Katz,[6] Yaan Kang,[6] Michael Kim,[6] Jason B. Fleming,[6] David Fogelman,[5] Milind Javle,[5] Anirban Maitra,[4,7] and Mien-Chie Hung[1,7,8,9,11,*]

[1]Department of Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Unit 108, 1515 Holcombe Boulevard, Houston, TX 77030, USA
[2]Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[3]Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[4]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[5]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[6]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[7]Graduate School of Biomedical Sciences, The University of Texas Health Science Center, Houston, TX 77030, USA
[8]Graduate Institute of Biomedical Sciences and Center for Molecular Medicine, China Medical University, Taichung 404, Taiwan
[9]Department of Biotechnology, Asia University, Taichung 413, Taiwan
[10]These authors contributed equally
[11]Lead Contact
*Correspondence: mhung@mdanderson.org
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SUMMARY

Pancreatic ribonuclease (RNase) is a secreted enzyme critical for host defense. We discover an intrinsic RNase function, serving as a ligand for epidermal growth factor receptor (EGFR), a member of receptor tyrosine kinase (RTK), in pancreatic ductal adenocarcinoma (PDAC). The closely related bovine RNase A and human RNase 5 (angiogenin [ANG]) can trigger oncogenic transformation independently of their catalytic activities via direct association with EGFR. Notably, high plasma ANG level in PDAC patients is positively associated with response to EGFR inhibitor erlotinib treatment. These results identify a role of ANG as a serum biomarker that may be used to stratify patients for EGFR-targeted therapies, and offer insights into the ligand-receptor relationship between RNase and RTK families.

INTRODUCTION

Epidermal growth factor receptor (EGFR) is an effective target for anticancer therapies in certain clinical settings (Avraham and Yarden, 2011; Lee et al., 2015). Notably, EGFR tyrosine kinase inhibitors (TKIs) have been approved to treat both lung and pancreatic cancers (Moore et al., 2007; Shepherd et al., 2005). EGFR-activating mutations identified in lung cancers have been well demonstrated to predict response to EGFR-TKI. Moreover, EGFR-mutated lung cancers are often addicted to EGFR activation and sensitive to EGFR-TKI, resulting in prolonged lifespan of a number of lung cancer patients (Rosell et al., 2012). However, those mutations are infrequent in PDAC (Tzeng et al., 2007; Wang et al., 2015), and EGFR-TKI erlotinib has shown

Significance

EGFR ligand ANG serves as a serum biomarker to predict response to erlotinib, an EGFR tyrosine kinase inhibitor, in PDAC. Knockdown of ANG demonstrates its oncogenic role and decreases sensitivity to erlotinib treatment *in vitro* and *in vivo*. High plasma ANG level in patients is positively associated with their response to erlotinib treatment in a small patient cohort, highlighting the interplay between ANG and EGFR in PDAC. This oncogene addiction effect may be advantageous for the development of a serum biomarker-guided target therapy in malignancies. The ANG-EGFR axis also opens an avenue toward our understanding of the ligand-receptor cognate signaling between RNases and RTKs, bridging two unrelated protein families via this ligand function of RNases.