Lapatinib–induced NF-kappaB activation sensitizes triple-negative breast cancer cells to proteasome inhibitors.

Meng-Chieh Yu, Yun-Ju Chen, Ming-Hsin Yeh, Ya-Ling Wei, Wen-Shu Chen, Jhen-Yu Chen, Chih-Yu Shih, Chih-Yen Tu, Chia-Hung Chen, Te-Chun Hsia, Shu-Hui Liu, and Wei-Chien Huang

Center for Molecular Medicine, China Medical University and Hospital
Graduate Institute of Cancer Biology, China Medical University

Introduction

Triple-negative breast cancer (TNBC), a subtype of breast cancer with negative expressions of estrogen receptor, progesterone receptor, and HER2, is diagnosed in younger women frequently and has poor prognosis for disease-free and overall survival. Due to the lack of known oncogenic driver for TNBC proliferation, clinical benefit from currently available targeted therapies is limited, and new therapeutic strategies are urgently needed.

Methods

Triple-negative breast cancer cell lines were treated with proteasome inhibitors in combination with lapatinib (a dual EGFR/HER2 tyrosine kinase inhibitor). Their *in vitro* and *in vivo* viability was examined by MTT assay, clonogenic analysis, and orthotopic xenograft mice model. Luciferase reporter gene, immunoblot, and RT-qPCR, immunoprecipitation assays were used to investigate the molecular mechanisms of action.

Results

Our data showed that NF-κB activation was elicited by lapatinib independent of EGFR/HER2 inhibitionin TNBCs. Lapatinib-induced constitutive activation of NF-κB involved Src family kinase (SFK)-dependent p65 and IκBα phosphorylations, and rendered these cells more vulnerable to NF-κB inhibition by p65 shRNA. Lapatinib but not other EGFR inhibitors synergized the anti-tumor activity of proteasome inhibitors both *in vitro* and *in vivo*. Our results suggest that treatment of TNBCs with lapatinib may enhance their oncogene addiction to NF-κB, and thus augment the anti-tumor activity of proteasome inhibitors.

Conclusions

These findings suggest that combination therapy of proteasome inhibitor with lapatinib may benefit TNBC patients.

Figure 1 Lapatinib induces NF-κB activation in an off-target manner.

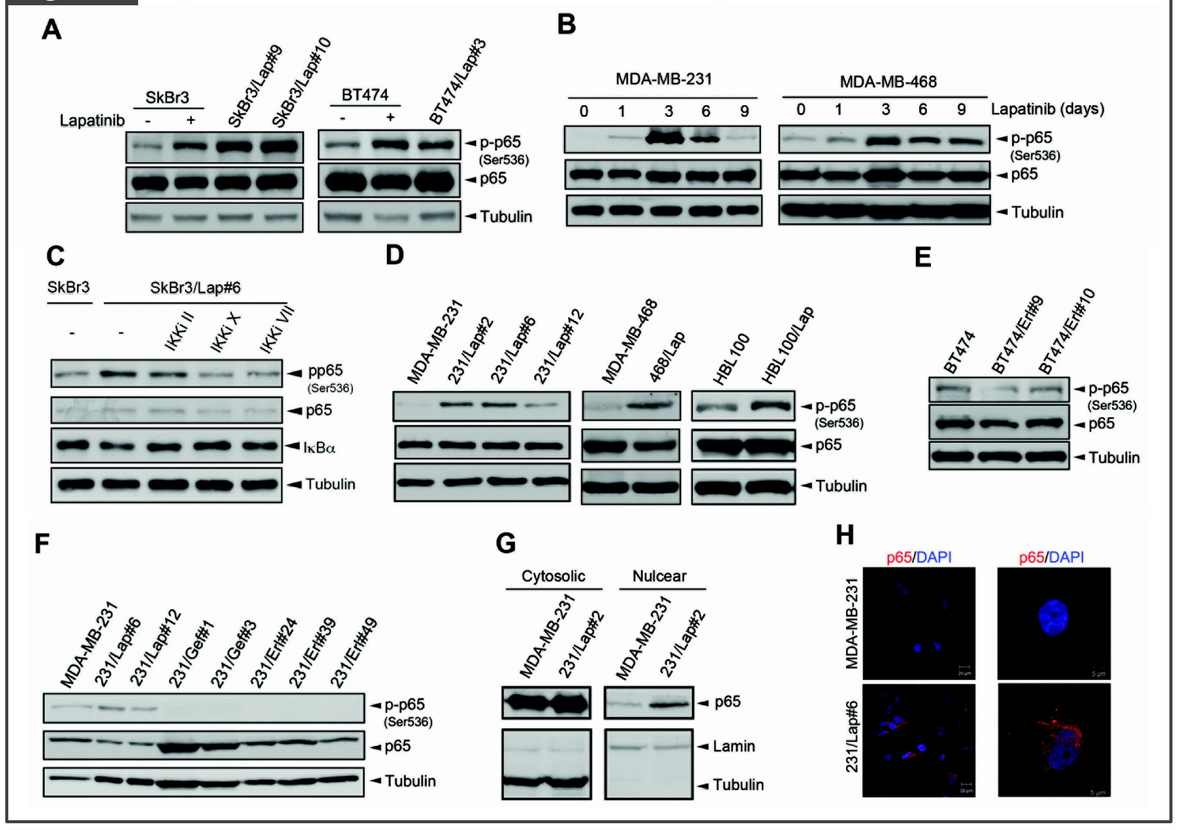

Figure 2 Expressions of NF-κB target genes are elevated by lapatinib in both HER2-positive and –negative breast cancer cells.

Figure 3 Off-target induction of NF-κB by lapatinib involves rapid IκBα turnover.

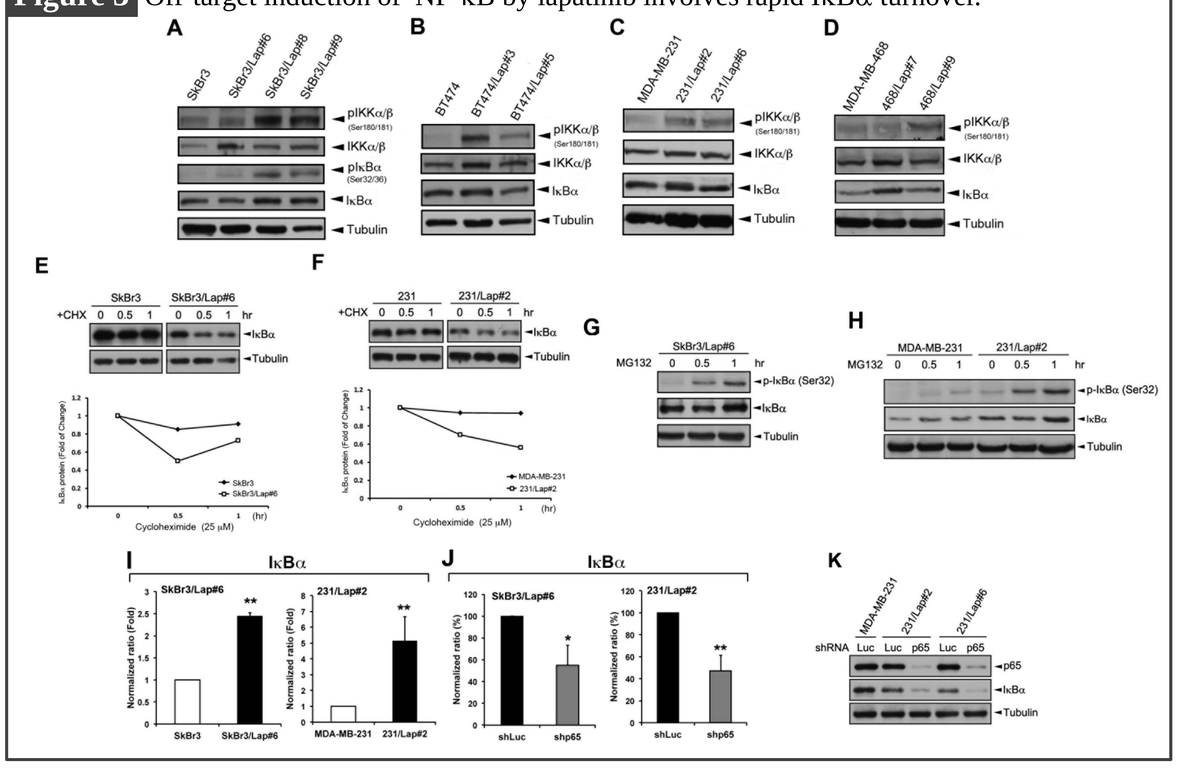

Figure 4 SFK activation contributes to off-target induction of NF-κB by lapatinib.

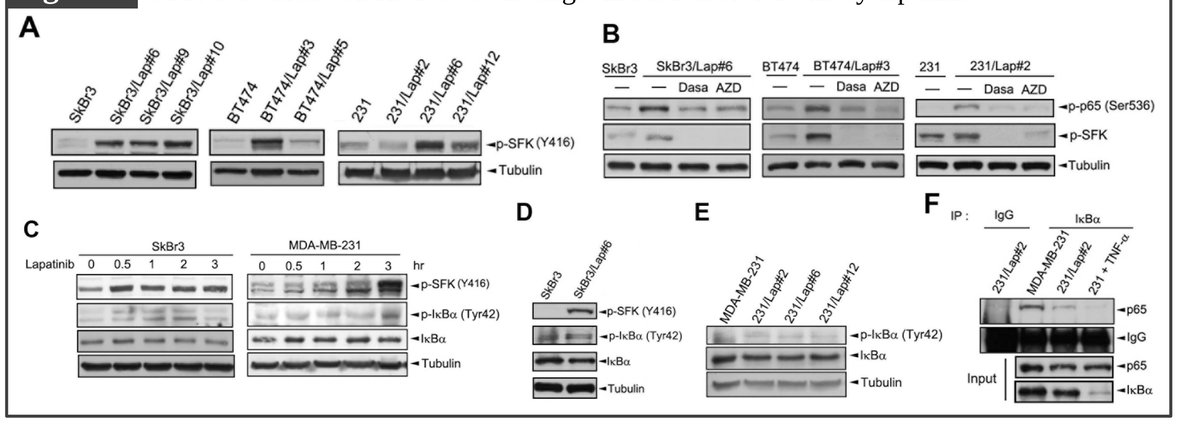

Figure 5 NF-κB functions as a critical regulator for cell survival in response to lapatinib treatment.

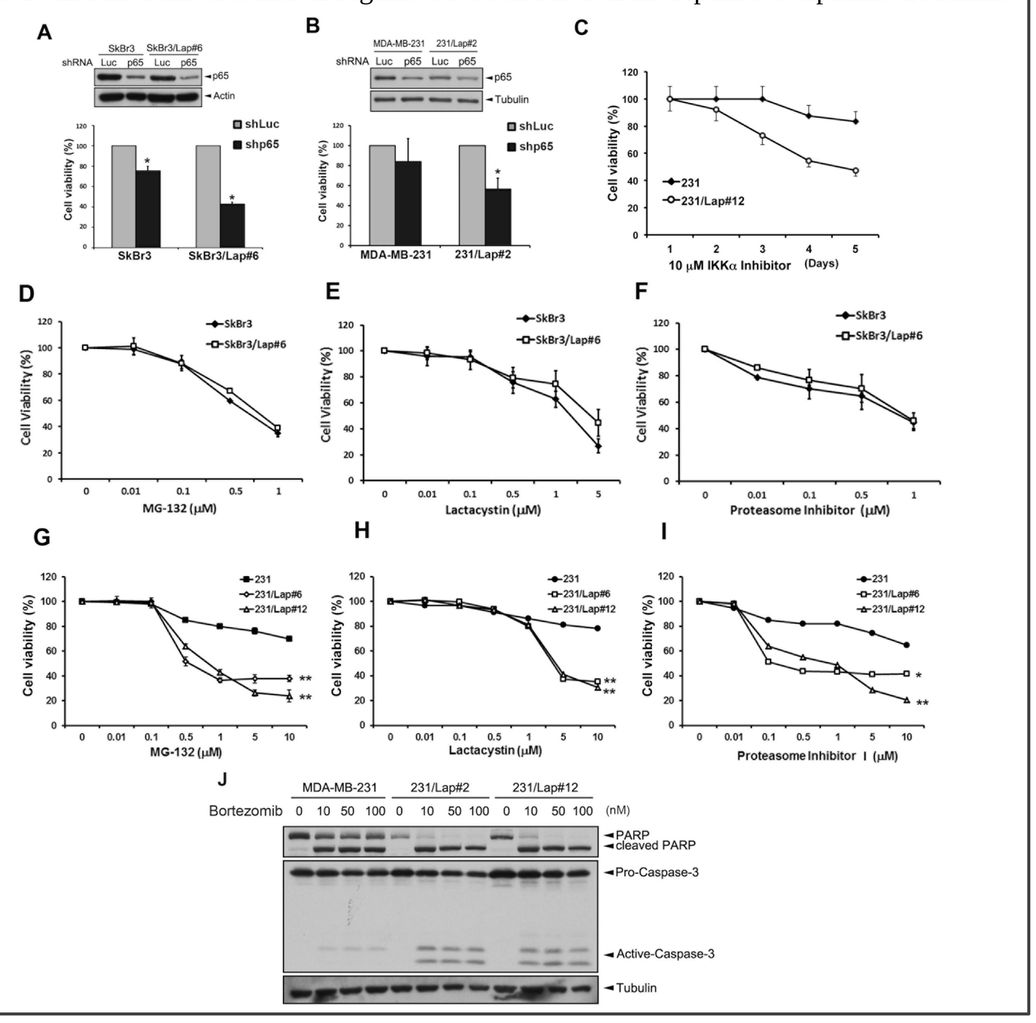

Figure 6 Co-treatment with lapatinib significantly enhances the anti-tumor activity of proteasome inhibitors in vitro and in vivo.