OFF-TARGET ACTIVITY OF LAPATINIB SENSITIZES TRIPLE-NEGATIVE BREAST CANCER CELLS TO PROTEASOME INHIBITORS THROUGH ACTIVATION OF NF-κB IN A SFK-DEPENDENT MANNER

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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 drivers for TNBC proliferation, clinical benefit derived from currently available targeted therapies for such patients is limited, and new therapeutic strategies are urgently needed. In this study, our data showed that NF-κB activation was elicited by lapatinib (a dual EGFR/HER2 tyrosine kinase inhibitor) in TNBCs. Independent of EGFR/HER2 inhibition, lapatinib-induced NF-κB constitutive activation involves Src family kinase (SFK)-dependent p65 and IκBα phosphorylations in TNBC cells, and thereby renders these cells more vulnerable to NF-κB inhibition by p65 shRNA. Co-treatment with lapatinib but not other EGFR inhibitors also synergized the anti-tumor activity of proteasome inhibitors both *in vitro* and *in vivo*. Our results suggest that treatment with lapatinib may enhance the oncogenic addiction of TNBCs to NF-κB, and thus augment the anti-tumor activity of proteasome inhibitor bortezomib. These findings suggest that the combination therapy of bortezomib and lapatinib may benefit TNBC patients.