Lapatinib-Mediated Cyclooxygenase-2 Expression via Epidermal Growth Factor Receptor/HuR Interaction Enhances the Aggressiveness of Triple-Negative Breast Cancer Cells

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Background & Aims

Lapatinib, a dual epidermal growth factor receptor (EGFR)/human epidermal growth factor receptor 2 (HER2) kinase inhibitor, showed clinical benefits in advanced HER2-positive breast cancer patients. Because some triple-negative breast cancers (TNBCs) frequently overexpress EGFR, the antitumor activity of lapatinib in such diseases was also tested. However, the results showed a worse event-free survival rate. It remains unknown whether and how lapatinib elicits the aggressiveness of such cancer cells. This study aimed to understand the therapeutic impact of lapatinib in TNBCs.

Materials & Methods

Lapatinib-resistant cancer cell clones were established by treatment with gradually increasing concentrations of lapatinib for over 1 month. The protein and RNA expression in TNBCs and lapatinib-resistant clones with western blot and real-time PCR. In vitro cell viability was measured using an MTT assay. Migration and Invasion abilities of TNBCs and their lapatinib-resistant clones were determined by wound healing and transwell migration assays. The animal model was established by injection TNBCs into the mammary gland in NOD-SCID mices.

Results

The lapatinib-increased motility was attributed by the elevation of EGFR through the downregulation of microRNA-7 and by the subsequent overexpression of cyclooxygenase-2 (COX-2). Strikingly, independent of its kinase activity, the elevated EGFR at least partly stabilized COX-2 expression by enhancing the binding of HuR to COX-2 mRNA.

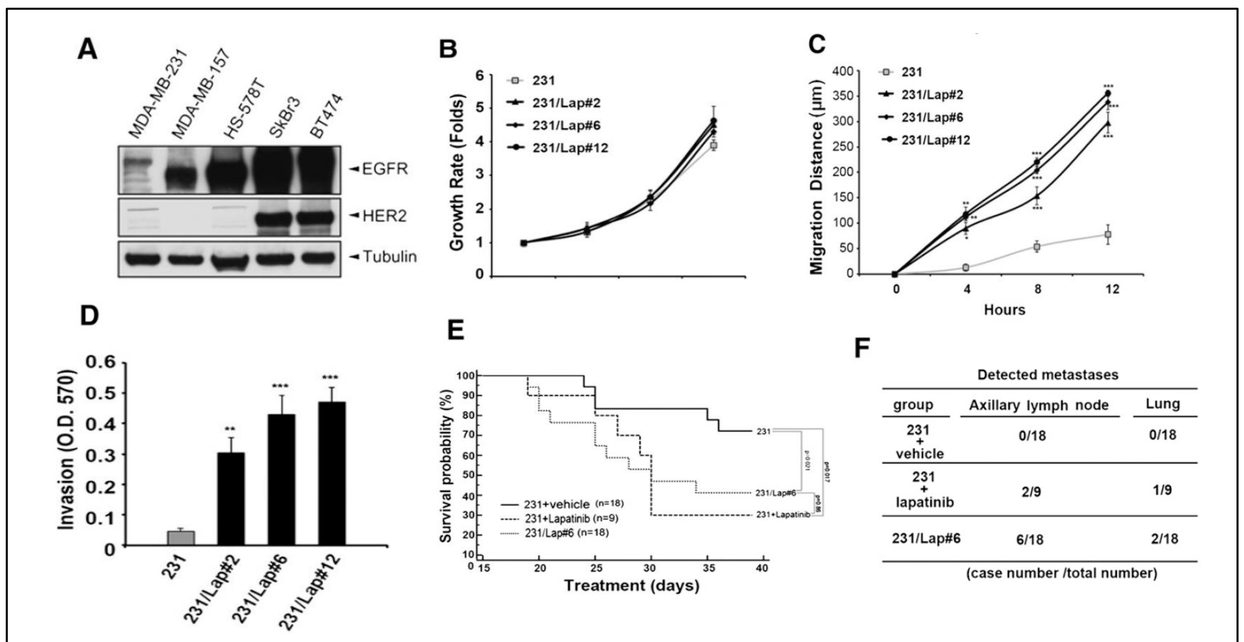

Figure 1. The effects of long-term treatment with lapatinib on migration and invasion of TNBC in *vitro* and in *vivo*.

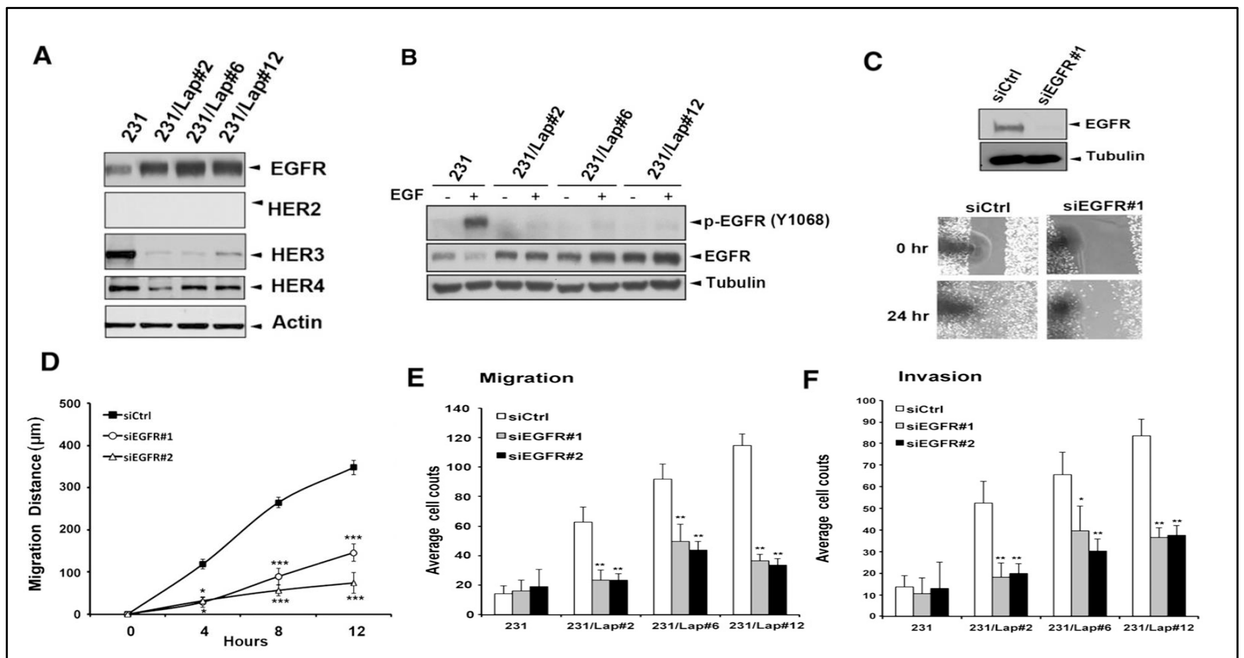

Figure 2. The involvement of increased EGFR expression in cell migration and invasion of lapatinib-resistant TNBCs.

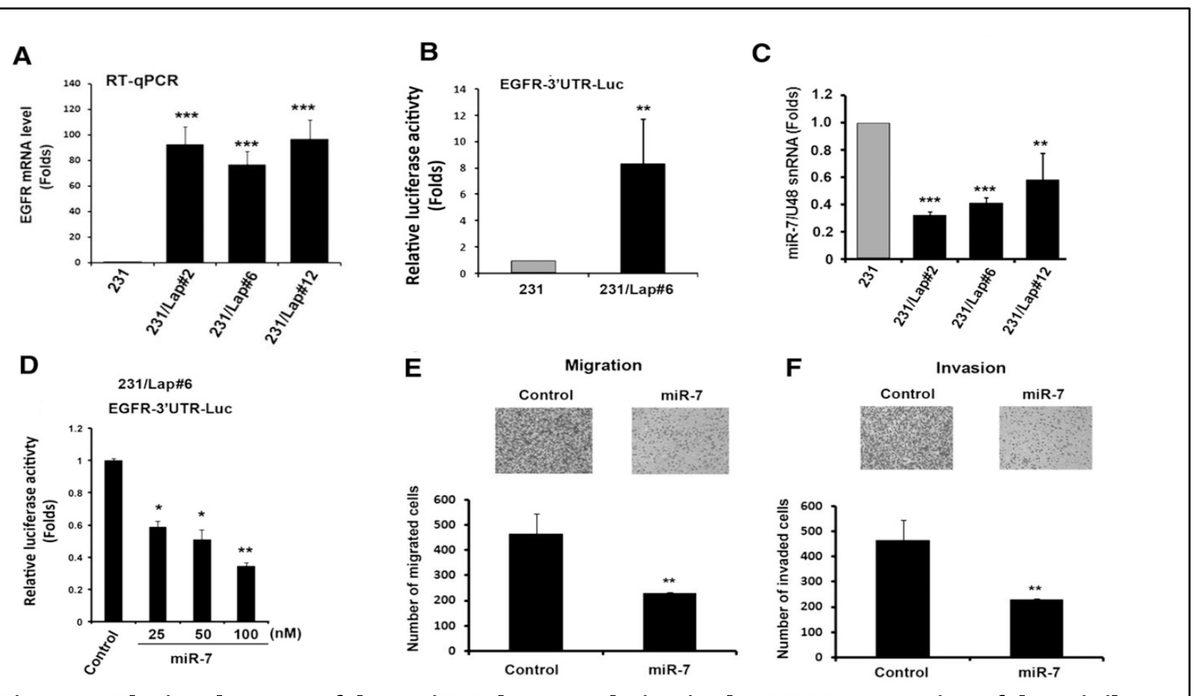

Figure 3. The involvement of has-miR-7 downregulation in the EGFR expression of lapatinib-resistant TNBCs.

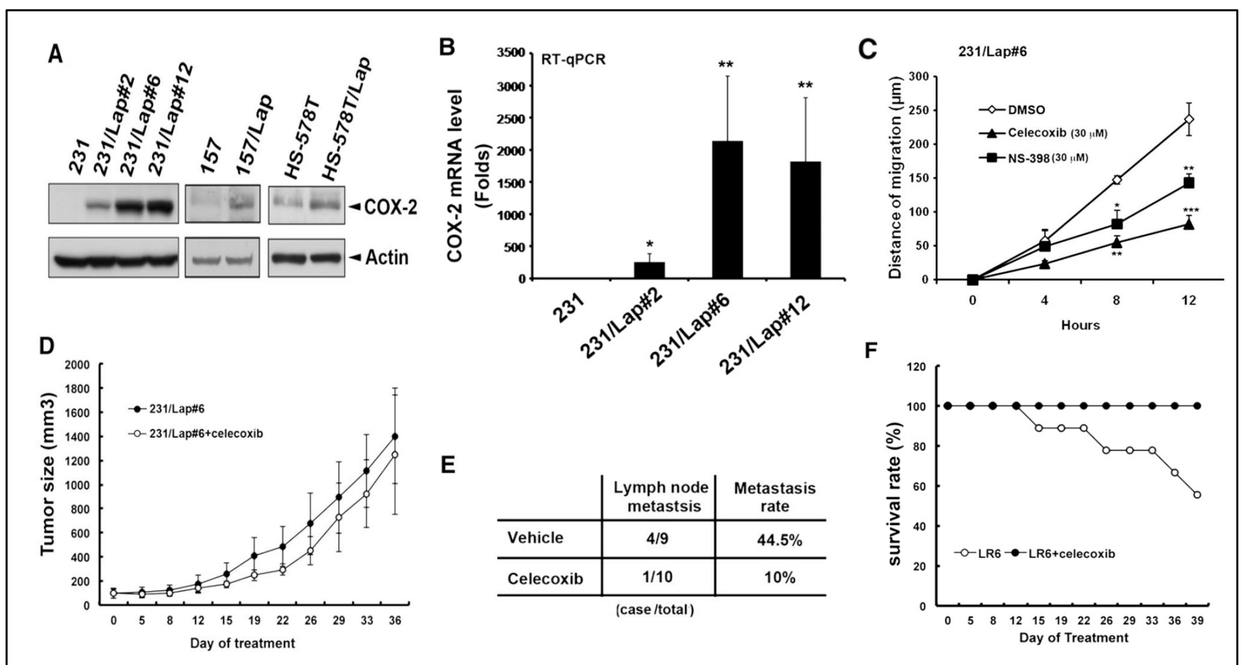

Figure 4. The effects of elevation of COX-2 expression on the cell migration of lapatinb-resistant TNBCs.

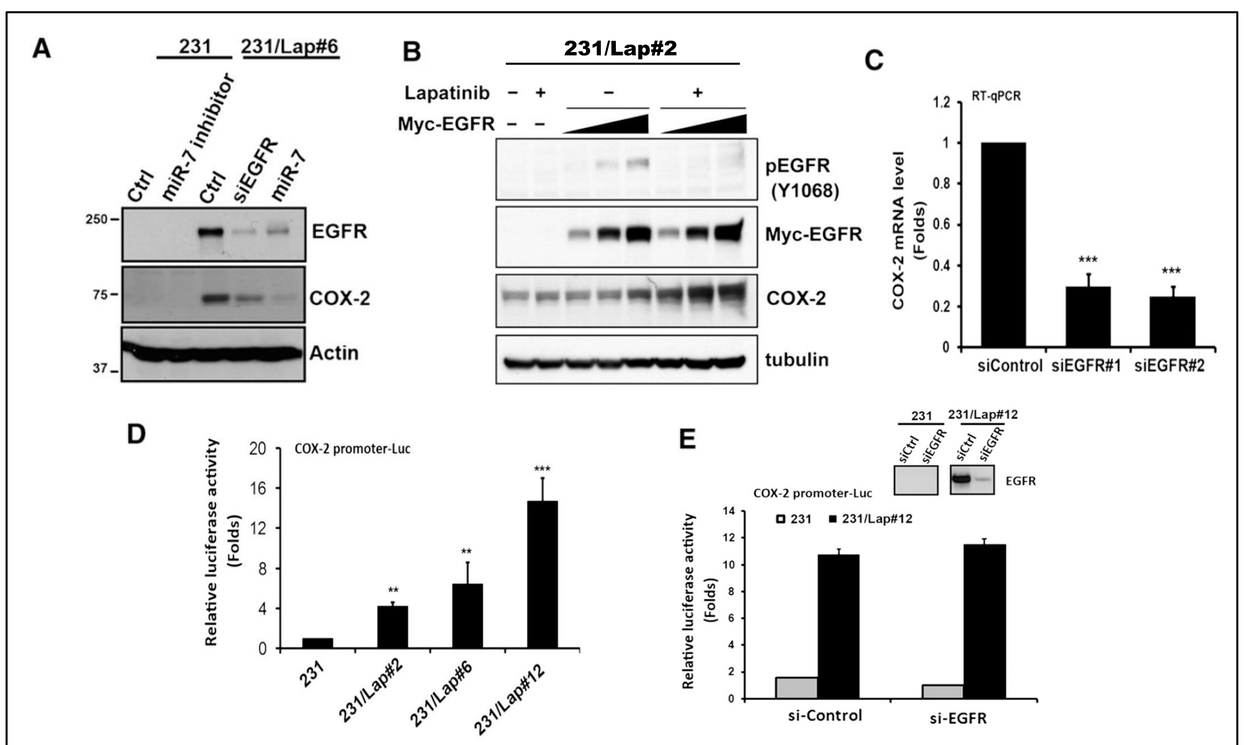

Figure 5. The role of EGFR in the mRNA stability and promoter activity of COX-2 in lapatinib-resistant TNBCs.

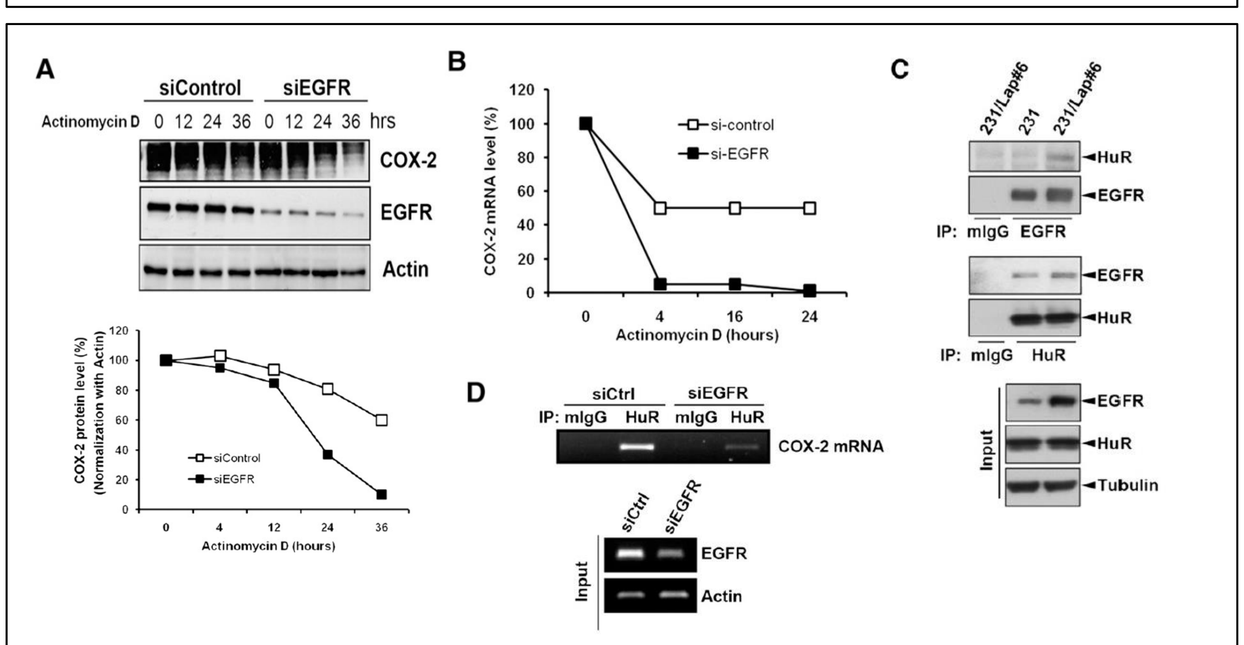

Figure 6. The involvement of EGFR in the binding of HuR to COX-2 mRNA in lapatinib-resistant TNBCs.

Conclusion

These data not only provided a potential explanation for the worse clinical outcome of TNBC patients who receive lapatinib-based treatment, but also shed new light on the molecular mechanism of COX-2 mRNA stabilization by EGFR in a kinase-independent manner.