Lapatinib enhances migration ability of triple-negative breast cancer cells through induction of Raf-1/MAPK-dependent interleukin-6 expression by downergulation of microRNA-7

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Abstract

Lapatinib, a dual epidermal growth factor receptor (EGFR) and HER2 tyrosine kinase inhibitor (TKI), has been approved for HER2-positive breast cancer patients. However, its therapeutic efficacy from EGFR inhibition in triple-negative breast cancer (TNBC) patients is limited even though overexpression of EGFR was frequently found in this disease. On the contrary, the enhancement of metastasis by lapatinib in TNBC cells has been further reported. In this study, we explored that the level of interleukin-6 (IL-6) was elevated in lapatinib-treated TNBC cells. Treatment with IL-6 antibody abolished the lapatinib-induced migration, suggesting that lapatinib enhances TNBC cell migration through induction of IL-6 expression. Mechanistically, the signaling axis of Raf-1/mitogen-activated protein kinases (MAPKs), c-Jun N-terminal kinases (JNKs), p38 MAPK, and activator protein 1 (AP-1) was activated in response to lapatinib treatment to mediate the induction of IL-6 expression. Furthermore, Raf-1 was demonstrated as a direct target of microRNA-7, and the down-regulation of miR-7 by lapatinib accounts for the activation of Raf-1 signaling pathway and the induction of IL-6 expression. Taken together, our results indicated that lapatinib enhanced the migration ability of TNBC cells through induction of IL-6 expression via the Raf-1, MAPK, JNK, p38, and AP-1 pathways by downregulating microRNA-7 expression.

Results

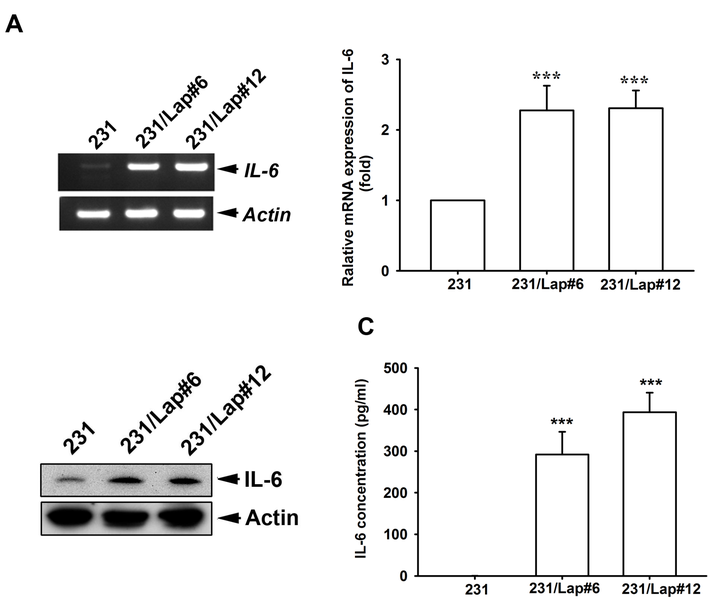


Figure 1. IL-6 expression was up-regulated in MDA-MB-231 TNBC cells with long-term treatment of lapatinib.

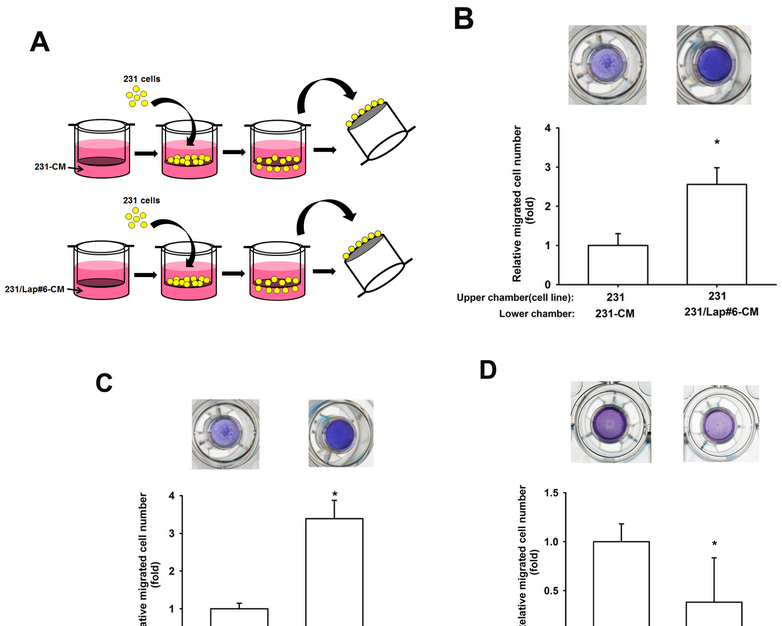


Figure 2. IL-6 was involved in the regulation of lapatinib-enhanced aggressiveness of 231 cells

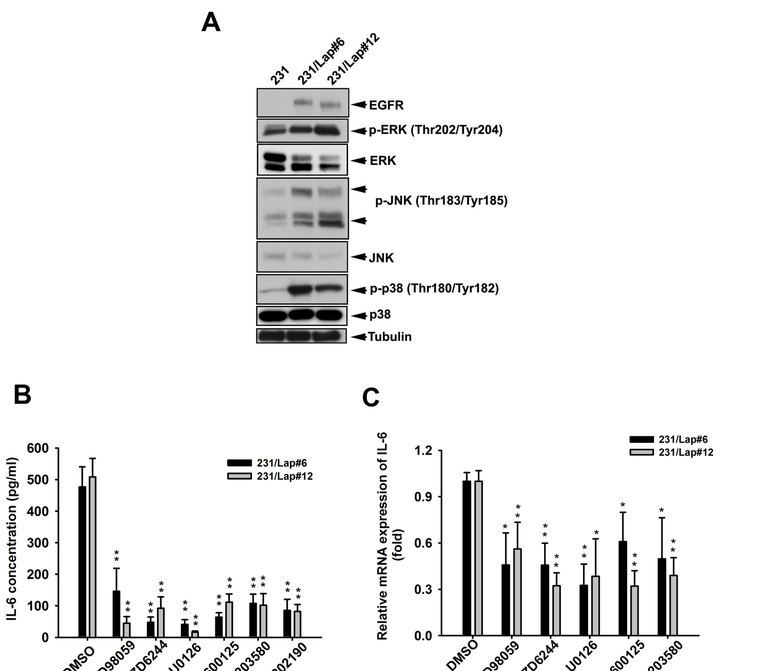


Figure 3. Lapatinib induced IL-6 expression through MAPK signaling pathways

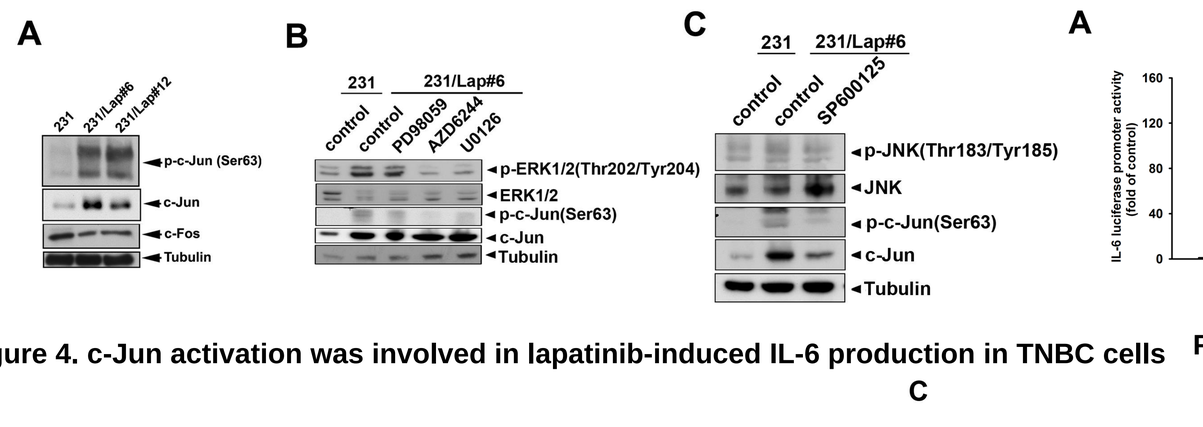


Figure 4. c-Jun activation was involved in lapatinib-induced IL-6 production in TNBC cells

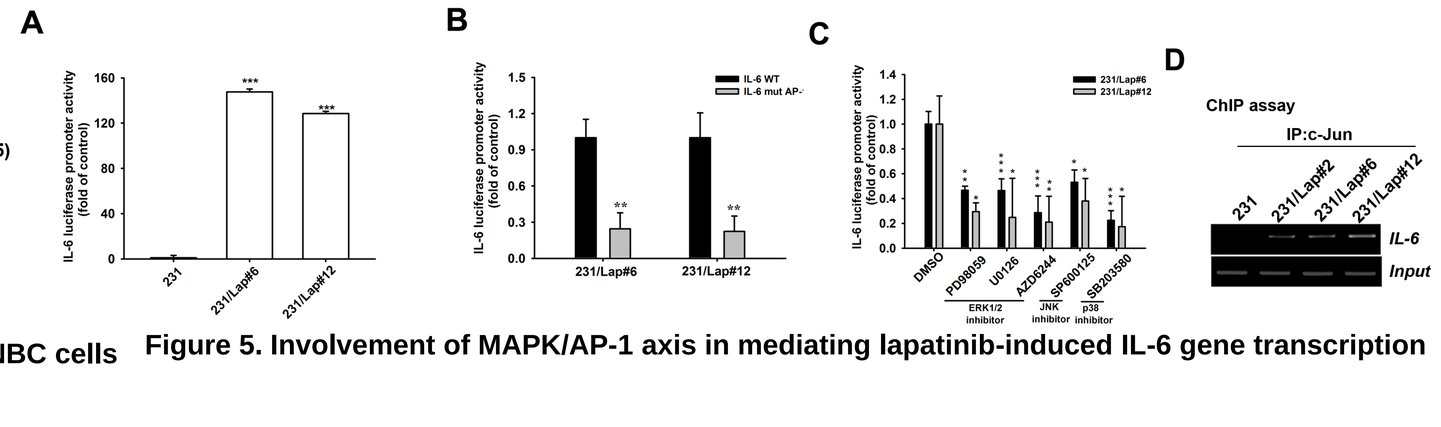


Figure 5. Involvement of MAPK/AP-1 axis in mediating lapatinib-induced IL-6 gene transcription

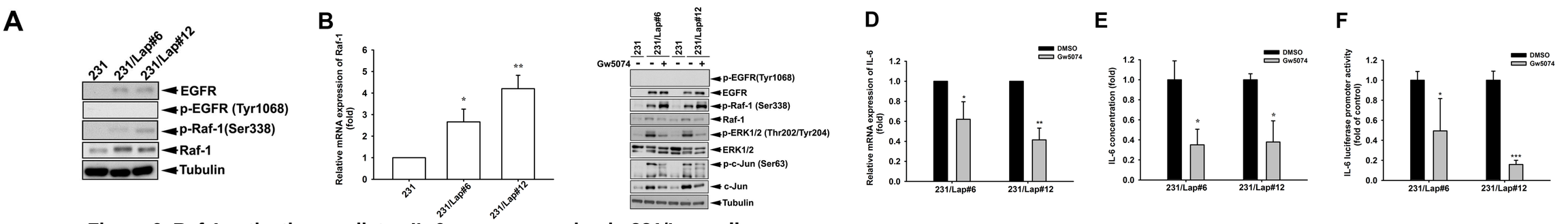


Figure 6. Raf-1 activation mediates IL-6 gene expression in 231/Lap cells

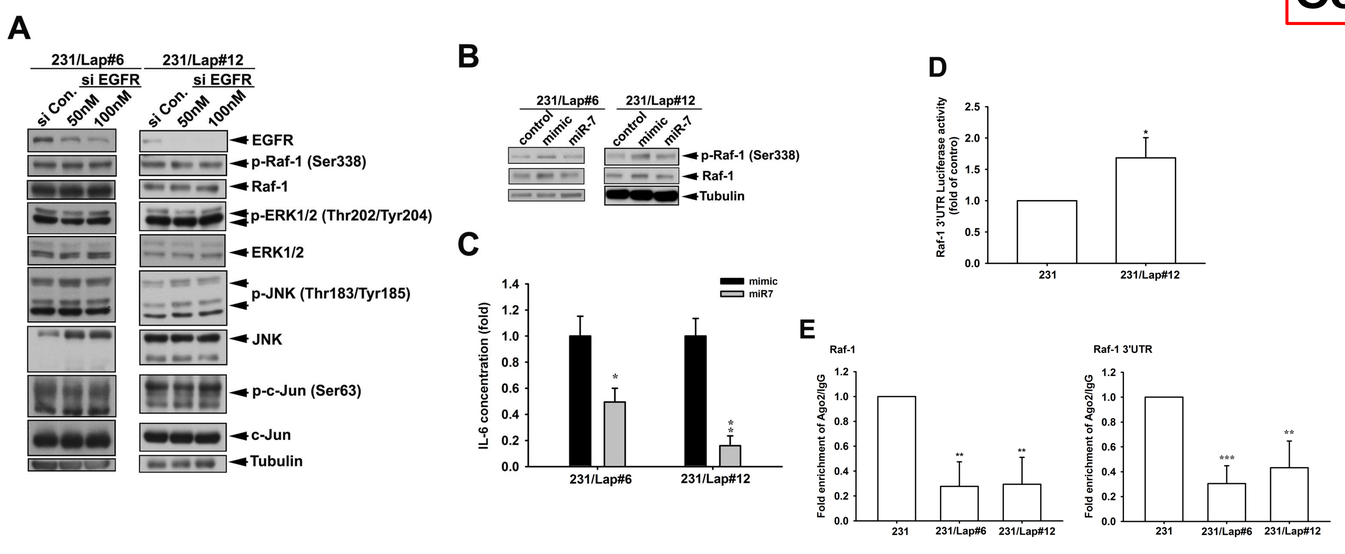
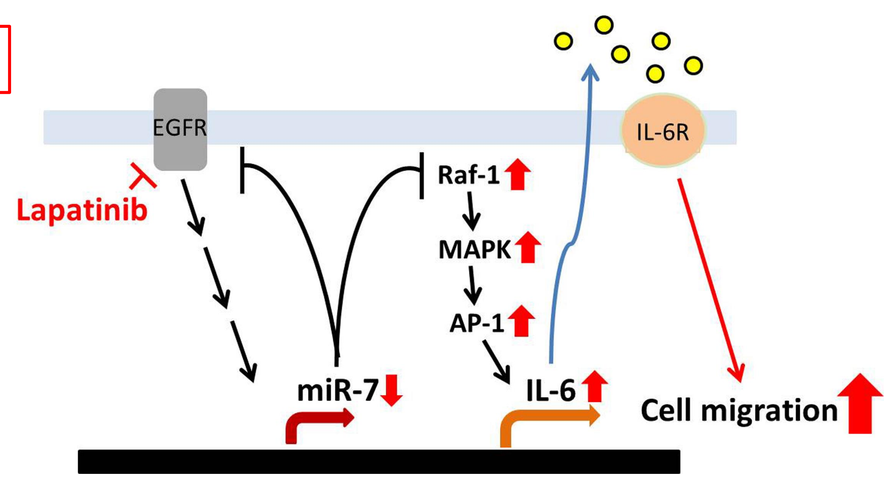


Figure 7. Elevation of Raf-1 expression in response to lapatinib is due to the de-repression from miR-7

Conclusion



Long-term treatment with lapatinib activates Raf-1/MAPK signaling pathways through downregulation of miR-7 expression. Then, the activated MAPKs induces expression and binding of c-Jun to IL-6 promoter, which leads to the production of IL-6. The secreted IL-6 in turn enhances the migration ability of TNBC cells.