Lapatinib induces IL-6 expression via MAPK pathway in triple-negative breast cancer cells

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Abstract

Lapatinib, the dual Epidermal growth factor receptor (EGFR) and HER2 tyrosine kinase inhibitor (TKI), have been tested in triple negative breast cancer (TNBC) patients in several clinical studies. However, limited clinic benefit was observed, and unexpectedly the metastatic ability of TNBC cells was even enhanced by these anti-cancer drugs in our previous studies. In this study, we found that induction of interleukin-6 (IL-6) expression was induced in lapatinib-treated cells to contribute to their increased ability of migration. Treatment of cells with the IL-6 antibody abolished the lapatinib-induced cell migration. In response to lapatinib treatment, Raf-1, Mitogen-activated protein kinases (MAPK), c-Jun N-terminal kinases (JNK), p38 mitogen activated protein kinase (p38 or p38-MAPK), and activator protein 1 (AP-1) signaling pathways were activated to mediate the induction of IL-6 level. Furthermore, downregulation of miR-7 was found to result in the lapatinib-induced activation of Raf-1signaling pathway and IL-6 expression. Taken together, our results indicated that lapatinib enhanced the migratory ability of TNBC through induction of IL-6 expression via the Raf-1, MAPK, JNK, p38, and AP-1 pathways by downregulating microRNA-7 expression.

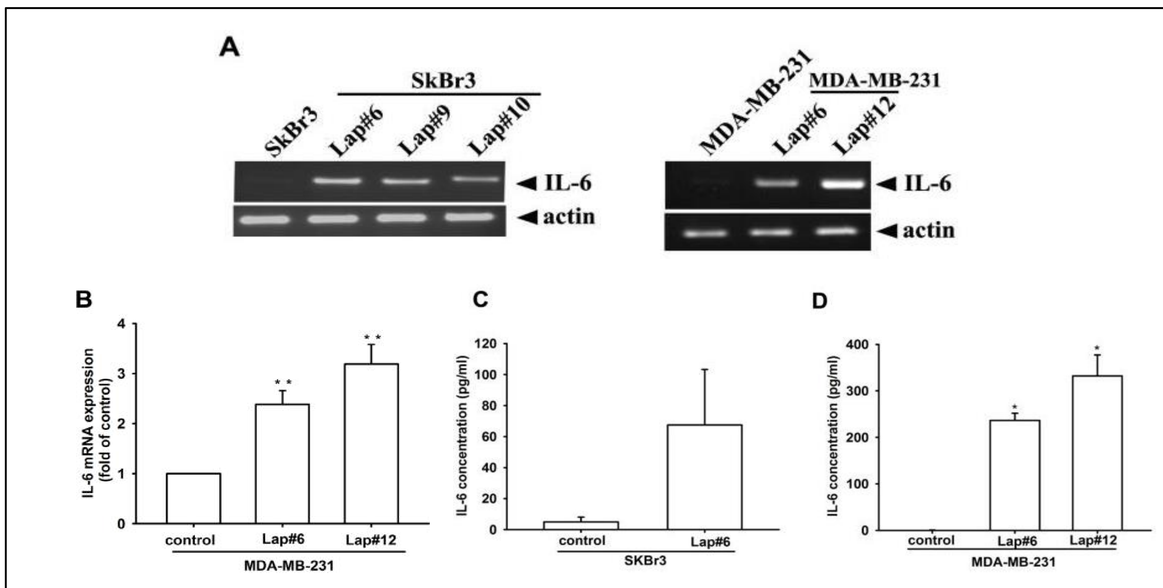


Figure 1. Treatment with lapatinib up-regulated IL-6 expression in both HER2-positive and -negative breast cancer cells.

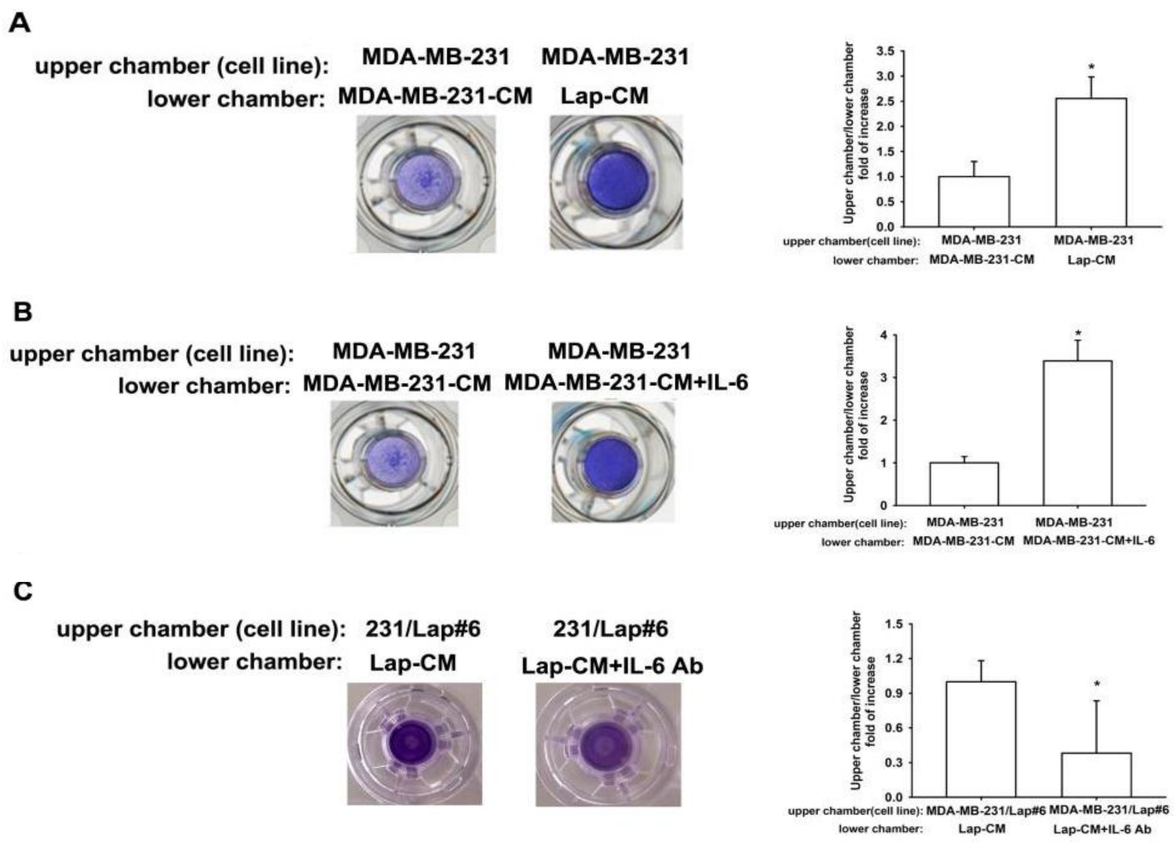


Figure 2. Up-regulation of IL-6 mediate lapatinib-induced migrationn.

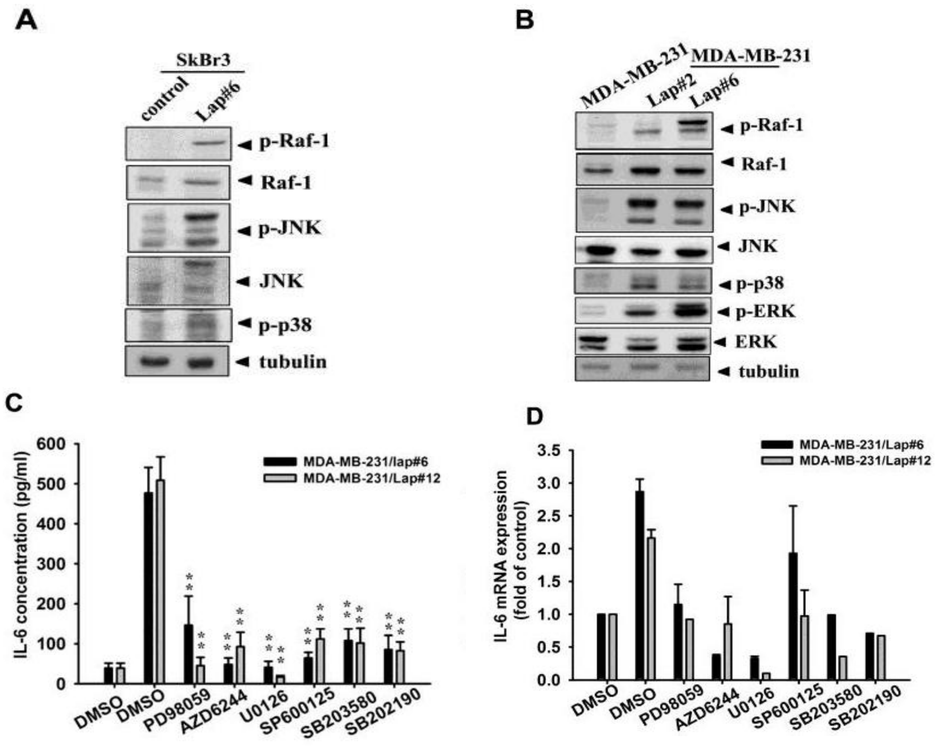


Figure 3. Lapatinib induced IL-6 expression through Raf-1 and MAP Kinase signaling pathway.

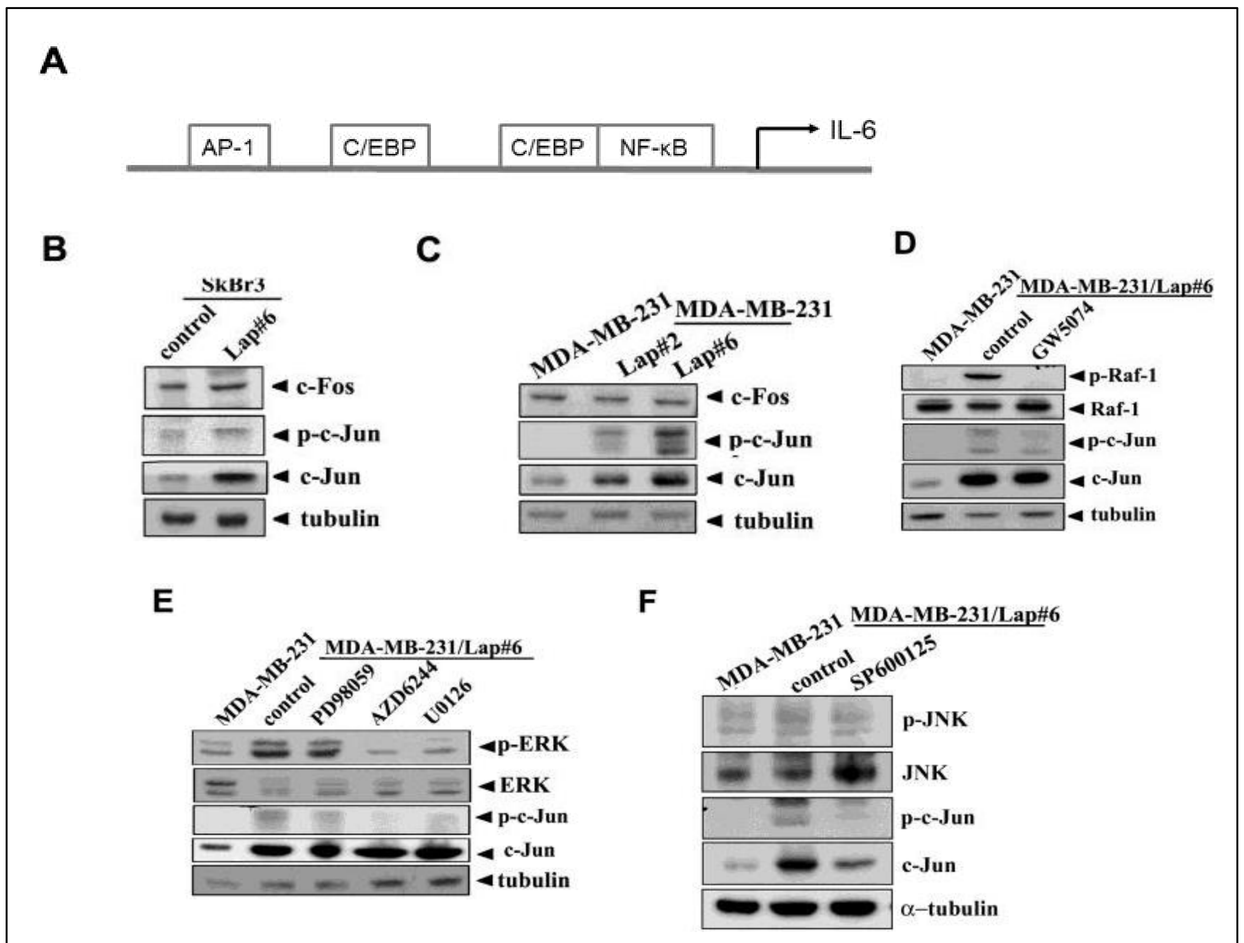


Figure 4. Lapatinib treatment induced c-Jun activation through Raf-1/MAPK signaling pathway.

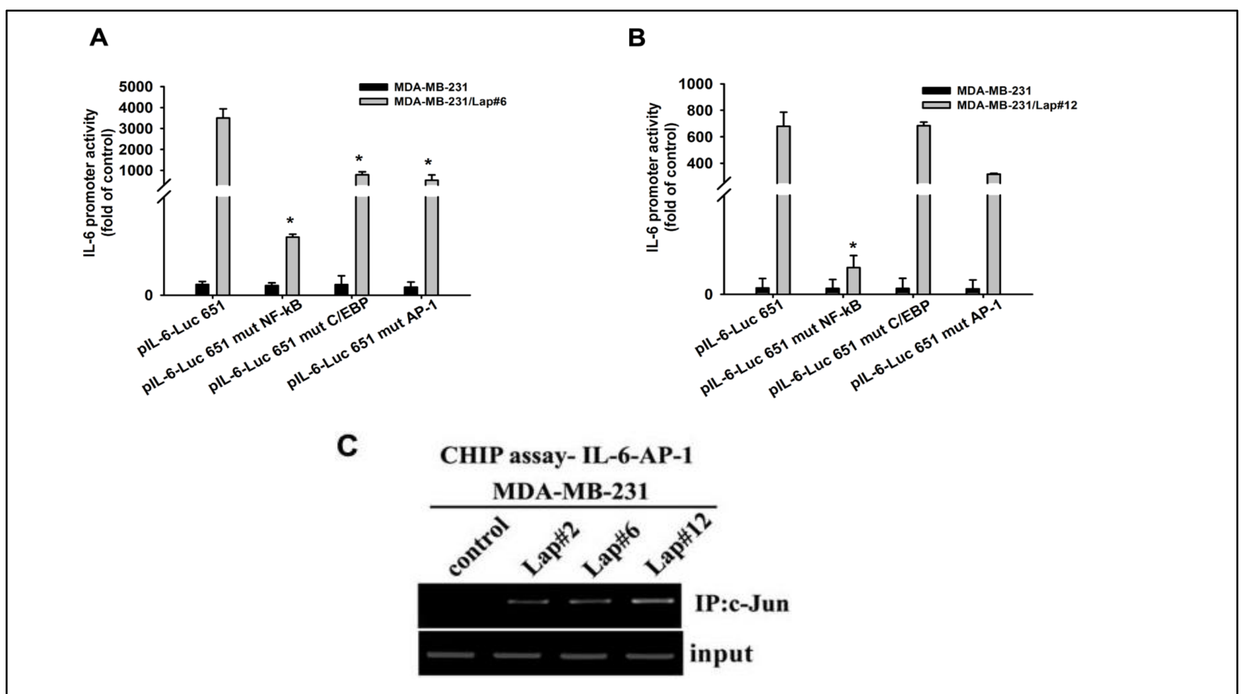


Figure 5. Raf-1/MAPK-activated AP-1 was involved in lapatinib-induced IL-6 expression.

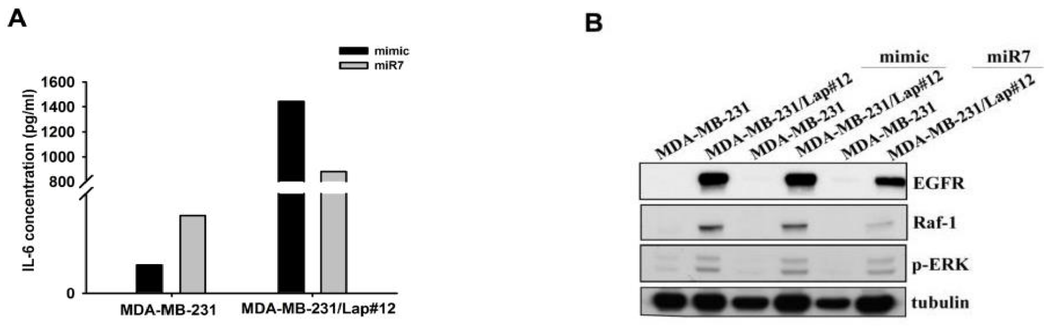
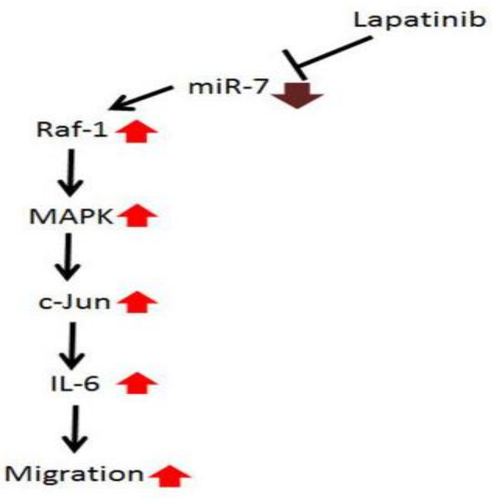


Figure 6. Overexpression of miR-7 down-regulated Raf-1/ERK1/2 signaling and reduced IL-6 expression in MDA-MB-231/Lap cells.

Conclusion



Acknowledgement

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