Trichostatin A Suppresses EGFR Expression through Induction of MicroRNA-7 in an HDAC-Independent Manner in Lapatinib-Treated Cells

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Abstract

Lapatinib, a dual EGFR/HER2 tyrosine kinase inhibitor, has been shown to improve the survival rate of patients with advanced HER2-positive breast cancers. However, the off-target activity of lapatinib in inducing EGFR expression without tyrosine kinase activity was demonstrated to render HER2-negative breast cancer cells more metastatic, suggesting a limitation to the therapeutic effectiveness of this dual inhibitor in HER2-heterogeneous tumors. Therefore, targeting EGFR expression maybe a feasible approach to improve the anticancer efficiency of lapatinib-based therapy. Inhibiti on of HDAC has been previously reported to epigenetically suppress EGFR protein expression. In this study, however, our data indicated that treatment with HDAC inhibitors trichostatin A (TSA), but not suberoylanilide hydroxamic acid (SAHA) or HDAC siRNA, can attenuate both protein and mRNA expressions of EGFR in lapatinib-treated triple-negative breast cancer cells, suggesting that TSA may suppress EGFR expression independently of HDAC inhibition. Nevertheless, TSA reduced EGFR 3 UTR activity and induced the gene expression of microRNA-7, a known EGFR-targeting microRNA. Furthermore, treatment with microRNA-7 inhibitor attenuated TSA-mediated EGFR suppression. These results suggest that TSA induced microRNA-7 expression to downregulate EGFR expression in an HDAC-independent manner.

Figure 1 TSA but not SAHA suppressed lapatinib-induced EGFR expression.

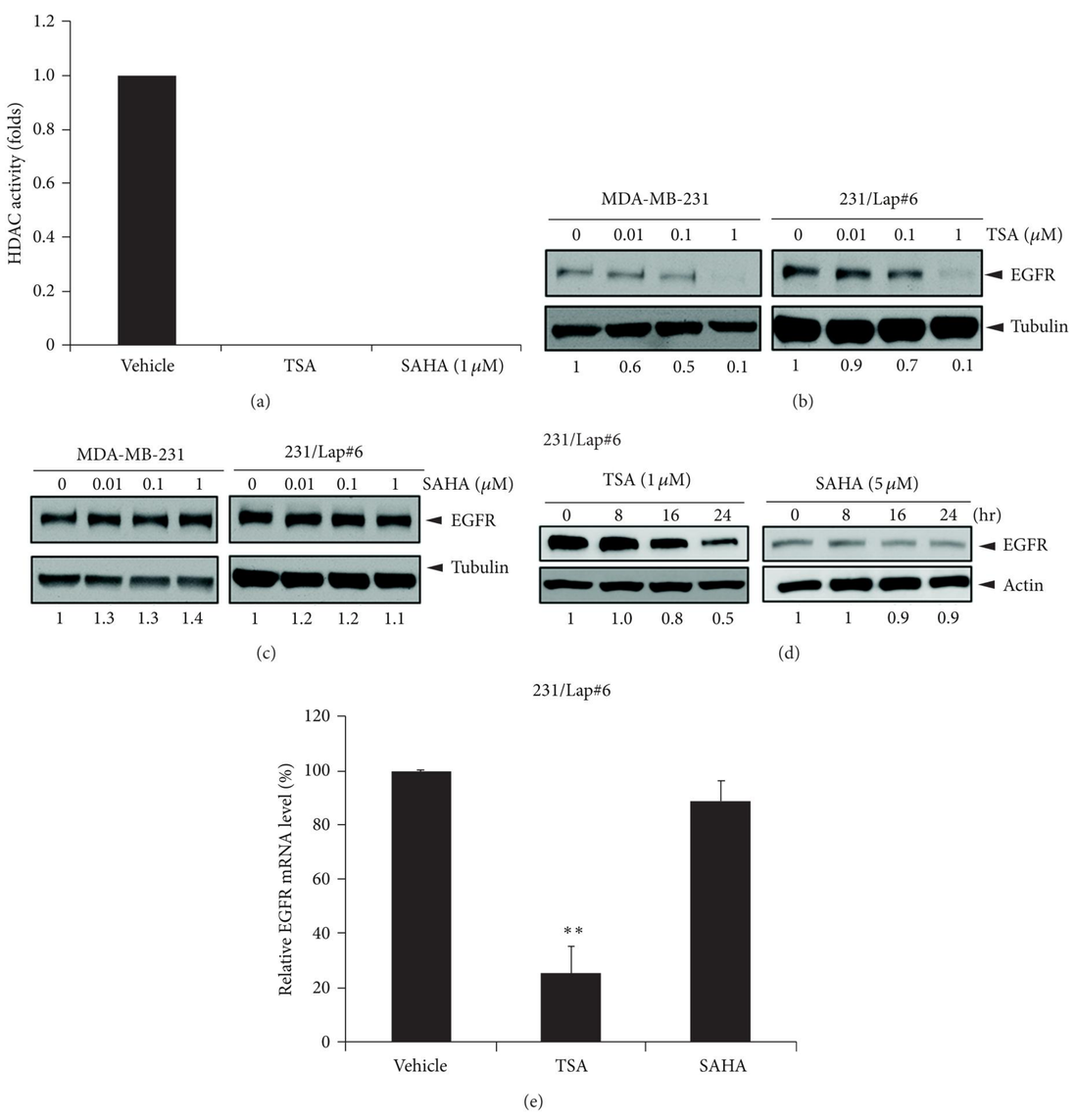


Figure 2 HDAC3 and HDAC7 expressions were elevated to cause histone hypoacetylations in lapatinib-treated MDA-MB-231 cell.

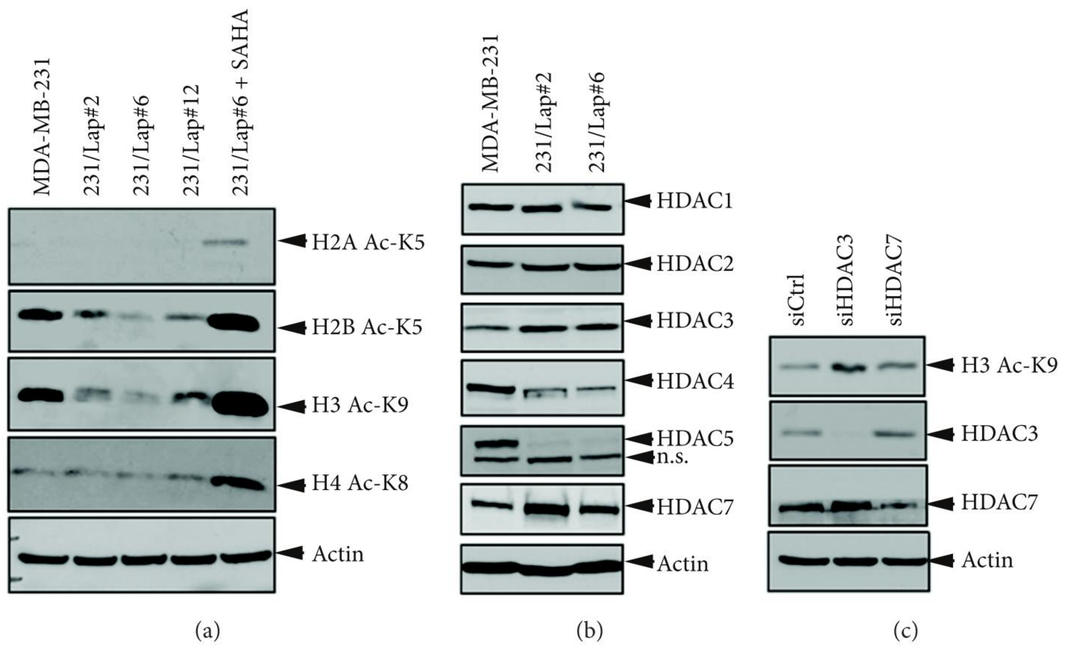


Figure 3 Silence of HDACs did not affect EGFR expression in lapatinib-treated MDA-MB-231 cells.

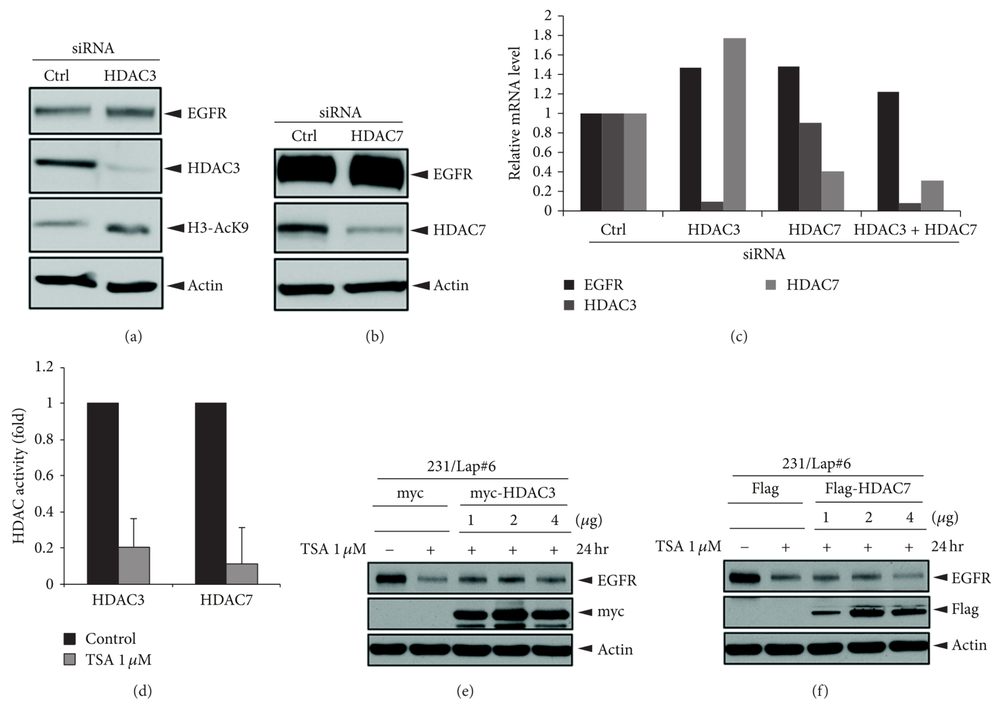


Figure 4 Proteasomal or lysosomal protein degradations were not involved in TSA-induced EGFR downregulation.

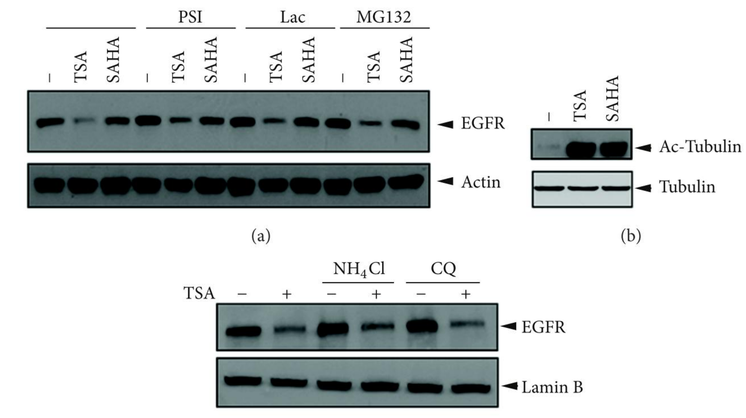


Figure 5 TSA suppressed the 3'UTR activity of EGFR mRNA.

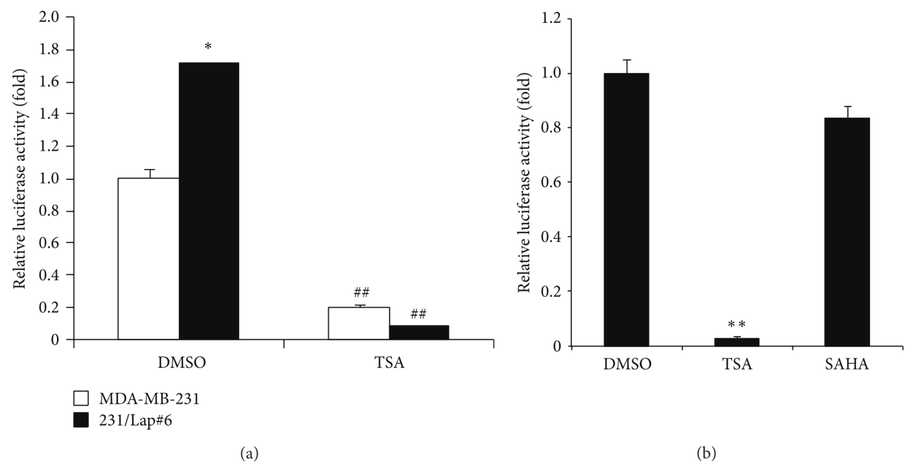
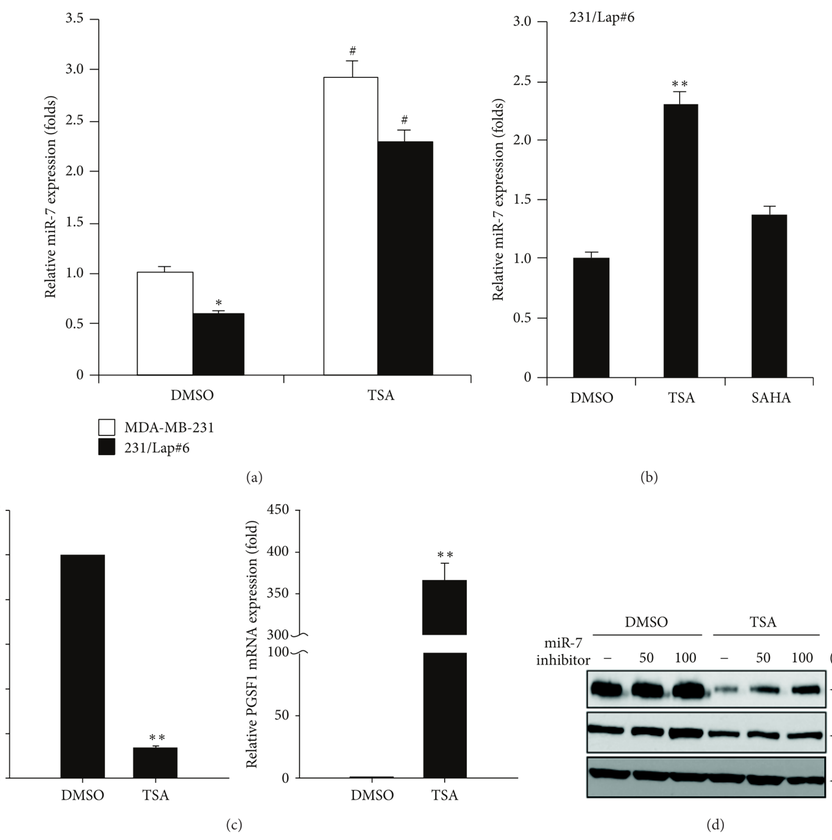


Figure 6 TSA induced miR-7 to suppress EGFR expression.



Conclusion

Our data uncovered a unique activity of TSA in inducing miR-7 expression. In distinction to its structural relative SAHA, TSA suppressed EGFR 3'UTR activity to attenuate its protein expression independently of HDAC inhibition in lapatinib-treated breast cancer cells. These results suggest a possible off-target activity of TSA in suppressing EGFR expression.

Acknowledgments

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