Elevation of Histone deacetylase mediates lapatinib-induced cell mobility of triple-negative breast cancer cells through COX-2 overexpression

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Abstract:

Background

To broaden its clinical use, the dual EGFR/HER2 tyrosine kinase inhibitor lapatinib was tested in triple-negative breast cancer (TNBC) according to its anti-EGFR activity, but unfortunately has been shown to worsen the progression-free survival rate. Our previous study further explored that lapatinib renders TNBC cells more metastatic via increasing COX-2 expression. However, the molecular mechanism underlying the induction of COX-2 expression by lapatinib remains unclear.

Observations

Here, we showed that up-regulation of histone deacetylases (HDACs), accompanying with the deacetylation of histone H3K9 and H2BK5, were found in the lapatinib-treated TNBC cells. Treatment with HDAC inhibitors (SAHA and TSA) dramatically reduced lapatinib-mediated cell migration and invasion through down-regulation of COX-2 expression transcriptionally. Both activations of AP-1 and NF-κB were observed and mediated the COX-2 gene expression in the lapatinib-treated TNBC cells. HDAC inhibition reduces AP-1 but not NF-κB activation, suggesting that elevation of HDACs mediates lapatinib-induced *COX-2* transcription through an AP-1-dependent manner.

Conclusions

Taken together, our results revealed that alterations of HDACs expression are involved in lapatinib-induced COX-2 expression and migration of TNBC cells and that co-treatment with HDAC inhibitors may improve the anti-tumor activity of lapatinib.