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Lapatinib resistance in nasopharyngeal carcinoma is mediated through Sirt2-modulated FOXO3 deacetylation

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Resistance to chemotherapy is an obstacle for the treatment of Nasopharyngeal Carcinoma (NPC). In this study, we found that highly metastatic NPC cells, 5-8F, treated with lapatinib exhibited an increase in pFOXO3 and FOXM1. In addition, Sirt2 protein levels were elevated in 5-8F cells compared with lowly metastatic, 6-10B, NPC cells. Inhibition of Sirt2 using a specific inhibitor and silencing by siRNA decreased cell viability to both inhibitor and lapatinib treatment. Moreover, our data suggested that Sirt2 mediated lapatinib resistance through FOXO3 deacetylation, which in turn led to degradation. Clonogenic assays revealed that 5-8F cells lacking Sirt2 exhibited reduction in long-term viability in response to lapatinib. Induction by lapatinib was attenuated in 5-8F stably expressing Sirt2 whereas its tumor suppressor FOXO3a increased its levels of acetylation in these cells. Furthermore, clonogenic capacity studies demonstrated that inhibition of Sirt2 in 5-8F and 6-10B cells conferred sensitivity to lapatinib, suggesting that Sirt2 reduced the lapatinib sensitivity through modulating FOXO3 acetylation and phosphorylation. Collectively, our data suggested that Sirt2 has a role in lapatinib sensitivity via targeting FOXO3 and that Sirt2 could be a useful biomarker and therapeutic target for lapatinib resistant cancer.

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