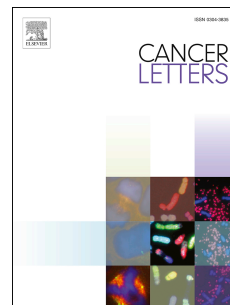


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Targeting autophagy by small molecule inhibitors of vacuolar protein sorting 34 (Vps34) improves the sensitivity of breast cancer cells to Sunitinib

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1 Resistance to chemotherapy is a challenging problem for treatment of cancer
2 patients and autophagy has been shown to mediate development of resistance. In
3 this study we systematically screened a library of 306 known anti-cancer drugs for
4 their ability to induce autophagy using a cell-based assay. 114 of the drugs were
5 classified as autophagy inducers; for 16 drugs, the cytotoxicity was potentiated by
6 siRNA-mediated knock-down of Atg7 and Vps34. These drugs were further evaluated
7 in breast cancer cell lines for autophagy induction, and two tyrosine kinase inhibitors,
8 Sunitinib and Erlotinib, were selected for further studies. For the pharmacological
9 inhibition of autophagy, we have characterized here a novel highly potent selective
10 inhibitor of Vps34, SB02024. SB02024 blocked autophagy *in vitro* and reduced
11 xenograft growth of two breast cancer cell lines, MDA-MB-231 and MCF-7, *in vivo*.
12 Vps34 inhibitor significantly potentiated cytotoxicity of Sunitinib and Erlotinib in MCF-
13 7 and MDA-MB-231 *in vitro* in monolayer cultures and when grown as multicellular
14 spheroids. Our data suggests that inhibition of autophagy significantly improves
15 sensitivity to Sunitinib and Erlotinib and that Vps34 is a promising therapeutic target
16 for combination strategies in breast cancer.

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