Sabutoclax overcomes drug resistance and eliminates cancer stem cells in breast cancer

Yunhui Hu, Jin Zhang

INTRODUCTION

Misregulation of BCL-2 family of proteins renders a survival signal to withstand cytotoxic anticancer drugs and is often found in drug resistant cells. The drug resistance phenotype is also associated with an enhancement of cancer stem cell-like (CSC) characteristics. Thus, inhibition of anti-apoptotic BCL-2 family proteins has been proposed as a possible antineoplastic strategy, and BCL-2 inhibitors are currently being clinically trailed in patients with leukemia, lymphoma or non-small cell lung cancer. However, the effects of BCL-2 inhibitors on drug resistant breast cancer have not yet been elucidated..

RESULTS

Sabutoclax shows potent cytotoxicity against both sensitive and chemoresistant breast cancer cells.

Sabutoclax eliminates the stem cell subpopulation of chemoresistant breast cancer cells.

Sabutoclax acts synergistically with chemotherapeutic agents both in vitro and in vivo.

Sabutoclax eliminates the stem cell subpopulation through down-regulation of the IL-6/STAT3 signaling pathway.

CONCLUSIONS

Sabutoclax partially overcomes the drug resistance phenotype of breast cancer cells by reactivation of apoptosis, mediated by the inhibition of several anti-apoptotic BCL-2 family proteins, and eliminates CSCs by abolition of the IL-6/STAT3 pathway. This offers a strong rationale to explore the therapeutic strategy of using sabutoclax alone or in combination for chemotherapy-nonresponsive breast cancer patients.