Inhibition of heat shock protein (Hsp) 27 potentiates the suppressive effect of Hsp90 inhibitors in targeting breast cancer stem-like cells

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Abstract

Heat shock protein (Hsp) 90 is an ATP-dependent chaperone and its expression has been reported to be associated with poor prognosis of breast cancer. Cancer stem cells (CSCs) are particular subtypes of cells in cancer which have been demonstrated to be important to tumor initiation, drug resistance and metastasis. In breast cancer, breast CSCs (BCSCs) are identified as CD24-CD44+ cells or cells with high intracellular aldehyde dehydrogenase activity (ALDH+). Although the clinical trials of Hsp90 inhibitors in breast cancer therapy are ongoing, the BCSC targeting effect of them remains unclear. In the present study, we discovered that the expression of Hsp90α was increased in ALDH+ human breast cancer cells. Geldanamycin (GA), a Hsp90 inhibitor, could suppress ALDH+ breast cancer cells in a dose dependent manner. We are interesting in the insufficiently inhibitory effect of low dose GA treatment. It was correlated with the upregulation of Hsp27 and Hsp70. By co-treatment with HSP inhibitors, quercetin or KNK437 potentiated ALDH+ cells toward GA inhibition, as well as anti-proliferation and anti-migration effects of GA. With siRNA mediated gene silencing, we found that knockdown of Hsp27 could mimic the effect of HSP inhibitors to potentiate the BCSC targeting effect of GA. In conclusion, combination of HSP inhibitors with Hsp90 inhibitors could serve as a potential solution to prevent the drug resistance and avoid the toxicity of high dose of Hsp90 inhibitors in clinical application. Furthermore, Hsp27 may play a role in chemoresistant character of BCSCs.