Abstract

Molecular-targeted therapies directed against human epidermal growth factor receptor 2 (HER2) are evolving for various cancers. Neratinib is an irreversible pan-HER tyrosine-kinase inhibitor, and was approved by the FDA as an effective drug for HER2-positive breast cancer. However, acquired resistance of various cancers to molecular-targeted drugs is an issue of clinical concern, and emergence of resistance to neratinib is also considered inevitable. In this study, we established various types of neratinib-resistant cell lines from *HER2*-amplified breast and lung cancer cell lines using various drug exposure conditions. Then we analyzed the mechanisms of emergence of the resistance in these cell lines and explored effective strategies to overcome the resistance. Our results revealed amplification of *YES1*, which is a member of the *SRC* family, was amplified in two neratinib-resistant breast cancer cell lines and one lung cancer cell line. Knockdown of *YES1* by siRNA and pharmacological inhibition of YES1 by dasatinib restored the sensitivity of the *YES1*-amplified cell lines to neratinib *in vitro*. Combined treatment with dasatinib and neratinib inhibited tumor growth *in vivo*. Moreover, this combination also induced downregulation of signaling molecules such as HER2, AKT and MAPK. Our current results indicate that *YES1* plays an important role in the emergence of resistance to HER2-targeted drugs, and that dasatinib enables such acquired resistance to neratinib to be overcome.