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DCZ3112, a novel Hsp90 inhibitor, exerts potent antitumor activity against HER2-positive breast cancer through disruption of Hsp90-Cdc37 interaction

Xiangling Chen, Peng Liu, Quanren Wang, Yun Li, Li Fu, Haoyu Fu, Jianming Zhu, Zhaoqiang Chen, Weiliang Zhu, Chengying Xie, Liguang Lou

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Abstract

Hsp90 regulates the stability of oncoproteins important in tumor development and progression, and represents a potential therapeutic target. However, all Hsp90 inhibitors currently in clinical trials target Hsp90 ATPase activity and exhibit low selectivity and high toxicity. In this study, we discovered a new Hsp90 inhibitor, DCZ3112, with a novel mechanism of action. DCZ3112 directly bound to the N-terminal domain of Hsp90 and inhibited Hsp90-Cdc37 interaction without inhibiting ATPase activity. DCZ3112 inhibited the proliferation predominantly in HER2-positive breast cancer cells, including those resistant to the classical Hsp90 inhibitor geldanamycin, which mainly targets ATPase. DCZ3112 produced synergistic *in vitro* activity in inhibiting cell proliferation, inducing G_1-phase arrest and apoptosis, and reducing AKT and ERK phosphorylation. Consistent with this, DCZ3112 alone inhibited the growth of HER2-positive BT-474 xenografts, and exhibited enhanced antitumor activity when combined with the anti-HER2 antibody trastuzumab. Importantly, DCZ3112 also significantly inhibited the growth of trastuzumab-resistant BT-474 cells, and combined treatment retained synergistic antitumor activity. Thus, our findings show that disrupting Hsp90-Cdc37 interaction may represent a promising strategy against HER2-positive breast cancer, especially those with acquired resistance to trastuzumab.