UPREGULATION OF METABOLISM ENZYMES MEDIATES ADC RESISTANCE IN A HER2-POSITIVE CANCER CELL LINE

1Dong Wang, 2Xiangnan Qiang, 1Zhixiang Zhang*, 1Qingyang Gu. 1WuXi AppTec, Inc., Shanghai, China; 2WuXi AppTec, Cambridge, MA, USA.

Background The receptor tyrosine kinase HER2 is overexpressed in approximately 20% of breast cancer, and its amplification is associated with reduced survival. Enhertu, also named DS8201a, is HER2-targeting ADC consisting of human HER2-targeted mAb trastuzumab and a derivative of DX-8951 (DXd), which are bound together by a maleimide glycylglycyl-l-alanyl-glycine (GGFG) peptide linker. Enhertu is approved for the treatment of patients with HER2-positive breast cancer, gastric cancer or HER2-mutant Non-Small Cell Lung Cancer. Acquired resistance has been a major obstacle to ADC treatment, and mechanisms remain incompletely defined.

Methods In the present study, CellTiter-Glo assay was used to detect viability of tumor cells treated with Enhertu, T-DM1, Dxd or DM-1. Binding of Enhertu with tumor cells was determined by flow cytometry. HER2 expression of tumor cells was analyzed by western blot and flow cytometry. Gene expression difference between drug resistant tumor cell and parental tumor cell was determined by RNA seq. Enhertu efficacy was measured in sub-cutaneous N87 xenografts after intravenous injection.

Results We established Enhertu resistant N87 cells (N87-R cells) in vitro. N87-R cells displayed no cross resistant to T-DM1, which is another HER2 targeting ADC. Then we tried Dxd and DM-1, which is the payload of Enhertu and T-DM1 respectively. Sensitivity to these payloads were consistent in N87-R cells and parental N87 cells. We also observed the HER2 expression level and the kinetics of binding were the same in N87-R cells and parental N87 cells. To investigate the mechanism of drug resistance, we conducted RNA seq of tumor cells. Increased expression of HER2 downstream signals containing PI3K-AKT signal and MAPK signal in N87-R cell were demonstrated by RNA sequencing. Gene expression difference was confirmed by qPCR. We combined PI3K inhibitor or MAPK inhibitor with Enhertu to treat N87-R cell and found increased sensitivity of tumor cells. Finally, we combined PI3K inhibitor or MAPK inhibitor with Enhertu in subcutaneous N87 xenograft and found the increased sensitivity of tumor cells.

Conclusions In this study, we established an Enhertu resistant N87 cell line and investigated the mechanism of drug resistance. Our results showed increased expression of HER2 downstream signals containing PI3K-AKT signal and MAPK signal lead to resistance of N87-R cells and inhibition of PI3K signal or MAPK signal reversed the resistance of tumor cells both in vitro and in vivo.

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