

gastrointestinal tumours, non-colorectal

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CELL GROWTH INHIBITION OF HER2 POSITIVE TRASTUZUMAB RESISTANT GASTRIC CANCER CELL LINES BY COMBINED INHIBITION OF PI3K/AKT/MTOR AND MAPK

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Aim: HER2 is a key genetic driver in gastric cancer development. The anti-HER2 antibody, trastuzumab, in combination with standard chemotherapy, increases survival in HER2 positive gastric cancer. However it is still unclear why HER2 overexpressing tumours are initially and subsequently nonresponsive to trastuzumab treatment. Our aim is to investigate the possible mechanisms involved in trastuzumab resistance.

Methods: A panel of human gastric and oesophago-gastric cancer cell lines (NCI-N87, KATO III, OE 19) were screened for EGFR, HER2, HER3, MAPK, PI3K/Akt/mTOR and 4EBP-1 expressions by Western Blot analysis. Cells were treated with increasing concentrations of selective inhibitors such as trastuzumab (HER2 inhibitor), erlotinib (EGFR inhibitor), MEK inhibitor (BAY-86-9766) or PIK3CA/mTOR inhibitor (GDC-0980) as a single agent and/or in combination. MTT analyses were performed to evaluate the inhibitory effect of each compound on cell growth.

Results: In all cancer cells EGFR, HER2, MAPK, AKT and 4EBP1 were expressed at different degree. Although high HER2 expression levels, trastuzumab caused growth inhibition only in OE19 cancer cell line with no activity showed in KATO III and NCI-N87, suggesting a trastuzumab intrinsic resistance. The combination of MEK and PIK3CA/mTOR inhibitors in cancer cell lines was able to inhibit cell growth of NCI-N87, KATOIII and OE19 with an IC₅₀ of 0.25 μM, 0.01 μM and 0.25 μM, respectively. The role of such therapeutic doublet in achieving cell growth inhibition was accompanied by significant reduction in the expression of AKT, pAKT, MAP, pMAP, 4EBP1 and p4EBP1 compared to control and trastuzumab treatment as revealed by Western Blot analysis.

Conclusions: The results of our in vitro study suggest that in HER2 trastuzumab resistant gastric cancer cell lines the double blockade of MAP and PI3K/Akt/mTOR pathways is able to induce significant growth inhibition suggesting a relevant crosstalk between the two pathways in this setting. On the basis of these preclinical data, new potential approaches could be explored in gastric cancer HER2 patients not responding to trastuzumab.

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