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Fibroblast Growth Factor Receptor (FGFR)3 sustains acquired resistance to trastuzumab in gastric cancer patients

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Background: Trastuzumab has been recently demonstrated as valuable treatment in HER2+ gastric cancer (GC). However the majority of patients who achieve an initial response to trastuzumab-based regimens develop resistance within 1 year of treatment. This study was aimed at identifying the molecular mechanisms responsible for this resistance.

Material and Methods: A GFP+/luciferase+, HER-2 positive, trastuzumab sensitive NCI-N87 GC orthotopic nude mouse model was used to select resistant models to this agent. Tumor growth was measured by using an IVIS Spectrum Imaging System. Differentially expressed transcripts between trastuzumab-resistant and sensitive GC cell lines were measured by Illumina whole-genome microarray, and tested for network and functional interrelatedness by IPA software. Expression of FGFR3, HER2, total AKT, phosphorylated (p)AKT, and ZEB1 was measured by immunohistochemical staining in pre- vs. post-treatment biopsies from GC patients progressing under trastuzumab-based treatment.

Results: NCI-N87 orthotopic tumor bearing mice were kept under treatment until the tumors suddenly recurred while on continuous therapy with trastuzumab. Four NCI-N87 trastuzumab resistant (N87-TR) cell lines were established from different excised tumors by repeated GFP flow cytometry sorting and their effective resistance was verified in vitro and in vivo. Microarray analysis showed the dowregulation of HER2, the induction of epithelial-to-mesenchymal transition, and indicated FGFR3 as one of the top 10 upregulated genes in N87-TR cell lines. We found a significant and consistent association of N87-TR gene expression profiles with the activation of the mTOR signaling. Accordingly, N87-TR cell lines showed significantly lower expression of all HER family members, E-cadherin and pERK1/2, and higher levels of FGFR3, vimentin, ZEB1, and pAKT than did sensitive control. In vitro, N87-TR cell lines demonstrated a higher sensitivity to the FGFR3 inhibitor dovitinib than did trastuzumab sensitive control. Treatment with dovitinib reduced the expression of pAKT, ZEB1, and migration in N87-TR cell lines. Oral dovitinib significantly reduced tumor burden and prolonged mice survival duration in N87-TR mouse models, whereas it was ineffective on trastuzumab-sensitive GC tumors. A significantly higher expression of FGFR3 and a lower expression of HER2 was observed in biopsies from GC patients progressing under trastuzumab-based therapies if compared with respective pre-treatment biopsies.

Conclusions: This study identified the FGFR3/AKT axis as an escape pathway responsible for trastuzumab resistance in GC, thus candidating dovitinib as potential agent to modulate this resistance.