Author's response to reviews

Title: MTDH Mediates Trastuzumab Resistance in HER2 Positive Breast Cancer by Decreasing PTEN Expression through an NF-kappa B dependent Pathway.

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Dear Dr. Solerà,

On behalf of all authors, I am pleased to submit our manuscript entitled: “MTDH Mediates Trastuzumab Resistance in HER2 Positive Breast Cancer by Decreasing PTEN Expression through an NFκB-dependent Pathway” for your consideration for publication in BMC Cancer.

Trastuzumab resistance is almost inevitable in the management of human epidermal growth factor receptor (HER) 2 positive breast cancer, in which phosphatase and tensin homolog deleted from chromosome 10 (PTEN) loss is implicated. Since metadherin (MTDH) promotes malignant phenotypes of breast cancer via diverse signaling pathways, we sought to define whether MTDH promotes trastuzumab resistance by decreasing PTEN expression.

We found that elevated MTDH expression indicated poor clinical benefit, shortened progression free survival time, and was negatively correlated with PTEN level both in HER2 positive breast cancer patients and trastuzumab-resistant SK-BR-3 (SK-BR-3/R) cells. MTDH knockdown restored PTEN expression and trastuzumab sensitivity in SK-BR-3/R cells, while MTDH overexpression prevented SK-BR-3 cell death under trastuzumab exposure, probably through IκBα inhibition and nuclear translocation of p65 which subsequently decreased PTEN expression. Synergized effect of PTEN regulation were observed upon MTDH and p65 co-transfection. Forced PTEN expression in SK-BR-3/R cells restored trastuzumab sensitivity. Furthermore, decreased tumor volume and Ki67 level as well as increased PTEN
expression were observed after MTDH knockdown in subcutaneous breast cancer xenografts from SK-BR-3/R cells, while the opposite effect were found in grafts from MTDH overexpressing SK-BR-3 cells.

These results suggest that MTDH overexpression confers trastuzumab resistance in HER2 positive breast cancer. MTDH mediates trastuzumab resistance, at least in part, by PTEN inhibition through an NFκB-dependent pathway, which may be utilized as a promising therapeutic target for HER2 positive breast cancer.

I confirm that the manuscript has not been published previously, either in whole or in part or in any other language, and is not being considered elsewhere. All authors participated in the writing and/or review of the manuscript and all have read and approved the final version for submission. There is no conflict of interests for all authors.

We believe our findings will be of interest to readers of the journal, and we look forward to hearing from you regarding its acceptability for publication.

Yours sincerely,

Cheng Du