Neuromedin U to increase IL-6 levels and to expand cancer stem cells in HER2-positive breast cancer cells.

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Background: Neuromedin U (NmU) is a neuropeptide belonging to the neuromedin family. Recently, a significant association between NmU signaling and cancer has been described, particularly correlated with increased aggressiveness and resistance to chemotherapy, although the mechanism through which it exerts this effect remains unexplained. **Methods:** HER2-positive breast cancer cells were stably transfected with NmU and IL-6 levels were measured by ELISA. Migration was evaluated in the presence of anti-NMUR antibodies by wound healing assays, while drug toxicity was assessed by the acid phosphatase assay. **Results:** Over-expression of NmU increases secreted levels of IL-6 (0 vs 0.303 ± 0.12 ng/μg, p = 0.04), a cytokine involved in promoting migration, expansion of the cancer stem cell population and drug resistance in breast cancer cells. NmU-transfected cells also show an increased proportion of cancer stem cells (CD44+/CD24-) (52.78 ± 5.765 vs 67.42 ± 5.172 in NmU-overexpressing cells, p = 0.07; fold change, 1 vs 1.31 ± 0.14, p = 0.00015) and increased expression of the lymphocyte activation inhibitor PD-L1, as detected by flow cytometry (49.50 ± 4.213 vs 60.06 ± 1.628, p = 0.0327); Furthermore, NmU over-expressing cells were shown to display enhanced resistance to antibody-dependent cell cytotoxicity mediated by Trastuzumab (47.13 ± 3.31% lysis of mock-transfected cells vs 36.46 ± 4.33% lysis in NmU-overexpressing cells, p = 0.05). Treatment with antibodies

that block NmU receptors NMUR1 and NMUR2 reduces cell migration and enhances toxicity of HER2-targeted drugs in NmU over-expressing cells, suggesting that interaction of NmU with NMUR1 and NMUR2 are necessary for its effects. **Conclusions:** Altogether, our results show a new mechanism of action of NmU in HER2-positive breast cancer cells that enhances resistance to HER2-targeted drugs and the anti-tumor immune response, and is at least partially mediated by IL-6. *Acknowledgements*: Science Foundation Ireland's funding of MTCI 08/SRC/B1410; HRB's Health Research Award [HRA-POR-2014-658]; Irish Cancer Society's Breast-Predict [CCRC13GAL]; and HEA's PRTLI Cycle 5 support of TBSI.
