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 1.3 ± 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 MTC1 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.

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