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Role of Jagged-1 in HER2-mediated notch inhibition in breast cancer

Clodia Osipo
Loyola University Chicago, USA

We have demonstrated that Notch1 is required for trastuzumab resistance in ErbB2 positive breast cancer. This indicates that ErbB2 suppresses Notch1 in breast cancer and therapeutic intervention targeting ErbB2 might have an unintended consequence which is aberrant up regulation of Notch1 which is a breast oncogene.However, the mechanism of action by which ErbB2 restricts Notch1 activation is unknown. In this current study, we investigated the role of cis- and trans-activation of Notch signaling by Notch ligands which are developmentally conversed to tightly regulate Notch activation. To address this hypothesis, we performed co-culture studies using fibroblasts expressing no Notch ligands or over-expressing human Jagged1 or Deltalike1 and ErbB2 positive breast cancer cells. We performed flow cytometry to isolate breast cancer cells after co-culture and extracted RNA to measure expression of *Notch* gene targets as a measure of Notch activity. The results showed that trastuzumab, Lapatinib, or ErbB2 knockdown increased overall Notch activation. Similarly, Co-culture with Jagged1-expressing fibroblasts increased overall Notch activation. However, Knocked down of Jagged1 in the breast cancer cells had little effect on ligand-induced Notch activation relieving the possibility of cis-inhibition. In contrast, Jagged1 knocked down abrogated trastuzumab-induced Notch activation in the breast cancer cells. These results suggest that ErbB2 might restrict Notch activation by preventing Jagged1-mediated trans activation of Notch and not by promoting cis-inhibition. Confocal immunofluorescence showed that Jagged1 is localized with Notch1 when ErbB2 is hyperactive but is trafficked to the cell surface in response to trastuzumab. K44ADynamin abrogated Jagged1 expression on the cell surface as measured by IF and surface biotinylation studies. Furthermore, K44ADynamin expression abrogated trastuzumab-induced Notch1 activation. Importantly, we measured growth consequences of Jagged1-mediated Notch activation in response to trastuzumab and found that Jagged1 is necessary for survival of ErbB2 positive breast cancer cells and trastuzumab resistance as measured by cell cycle analysis and Annexin V staining. These results taken together indicate that ErbB2 restricts Notch by limiting Jagged1-mediated trans-activation.

Biography

Clodia Osipo is an Associate Professor of Pathology/Oncology Institute and the Co-Leader of the Breast Cancer Translational Program at the Cardinal Bernardin Cancer Center of Loyola University Chicago. The focus of her research career has been to elucidate critical mechanisms responsible for drug resistant breast cancer. The goal of the research laboratory is to identify these critical survival and proliferative pathways to provide novel targets for new therapeutic interventions. Currently, the laboratory is focused on the role and contribution of the Notch signaling pathway in drug resistance to anti-hormonal and anti-ErbB-2 therapies. The critical research objective is to identify, validate, and test novel therapeutics targeting Notch signaling with the expectation of preventing breast tumor resistance, recurrence, progression, and ultimately death-associated with Notch-mediated drug resistance.

cosipo@lumc.edu