The kisspeptin signalling pathway and its role in breast cancer biology

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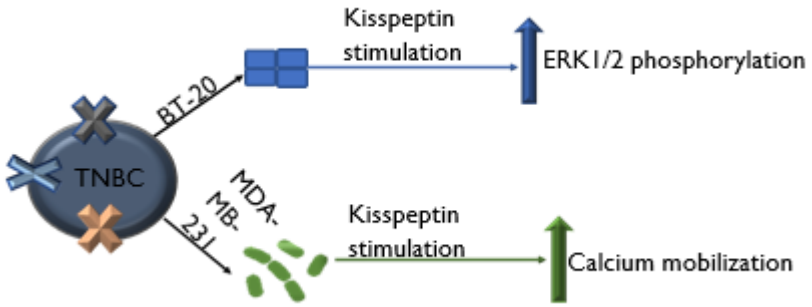

Figure 1: Kisspeptin elicits biased signalling in the triple negative breast cancer (TNBC) cell lines, BT-20 and MDA-MB-231. When stimulated with 100 nM kisspeptin-10, there is an increase in ERK1/2 phosphorylation in BT-20 cells. Whereas in the MDA-MB-231 cell line, there is an increase in intracellular calcium.

Introduction

Kisspeptin is a neuropeptide that was first identified as a metastasis suppressor in human melanoma. It is the endogenous ligand for the G-protein coupled receptor, KISS1R. Apart from melanoma, kisspeptin hasbeen shown to inhibit metastasis in pancreatic, lung, bladder, and ovarian cancers. However, in breast cancer, controversy exists as pro- and anti-metastatic properties have been observed after kisspeptin stimulation suggesting some level of biased signalling. This study aims to shed light on these contradictory observations by investigating the ability of the endogenous receptor to direct intracellular signalling pathways in response to kisspeptin binding in different breast cancer cell lines and how these affect cell proliferation, migration, and invasion.

Methodology

Two triple negative breast cancer lines, the non-metastatic BT-20 and metastatic MDA-MB-231 were compared. KISS1R expression in both cell lines was assessed and western blot analysis was used to assess ERK1/2 and Akt/PKB phosphorylation and β-arrestin1/2 expression. Several inhibitors were used to identify pathway components. Calcium mobilisation was assessed using fluo-3 AM and cell migration was assessed using scratch assays.

Results

Both cell lines express endogenous KISS1R. ERK1/2 and Akt phosphorylation only occurs in the BT-20 cellline after kisspeptin stimulation with ERK1/2 phosphorylation occurring late in a β-arrestin1/2 dependent manner. Calcium mobilisation occurs at a high rate in the MDA-MB-231 cell line in a PLC dependent manner while only minor calcium mobilisation was observed in the BT-20 cell line. Similarly, MDA-MB-231 cell migration increased after stimulation while no effect was observed in BT-20 cells.

Discussion and Conclusion

Our results show that although the two breast cancer cell lines both express endogenous KISS1R, kisspeptin elicits different signalling responses suggesting that there is cell context bias. This biased signalling seems to result in different physiological outputs with only the MDA-MB-231 cells increasing migration. In conclusion, our data goes some way to explain the contrasting effects observed in breast cancer after kisspeptin stimulation.

Keywords: Breast cancer, BT-20, ERK1/2, kisspeptin, MDA-MB-231.