ISGE
GYNECOLOGICAL ENDOCRINOLOGY
THE 18TH WORLD CONGRESS
7-10 MARCH 2018 FLORENCE, ITALY

GPER1 Promotes Estrogen Receptor Negative Breast Cancer Cells Migration and Invasion via Nongenomic Activation of c-Src/NF-?B/Focal Adhesion Kinase Cascade

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Context: Breast cancer metastasis accounts for the majority of deaths from breast cancer. Currently endocrine therapy resistance in ER-positive (ER+) breast cancer remains a major clinical issue. Moreover, ER-negative (ER-) breast cancer are often associated with distant recurrence and death. G-protein-coupled estrogen receptor GPER1 participates endocrine therapy resistance and controls breast cancer malignant progress, while the detailed mechanism remains largely unknown.
Objective: To investigate the role of GPR30 in estrogen-promoted breast cancer cell migration and invasion. Moreover, the molecular mechanism under the estrogen nongenomic effets was investigated.
Main Outcome Measures: immunofluorescence, transfection experiments, cell proliferation, migration, and western blot were performed.
Results: In this study, we investigated the role and mechanism of GPER1 on the activation of focal adhesion kinase (FAK) by using breast cancer cell lines with ER+ or ER-. In cultured SK-Br-3 cells (ER?-/?-/GPER1+), both 17?-estradiol (E2) and GPER1 agonist G1 resulted in FAK phosphorylation in a nongenomic manner. The signalling cascade implicated in this action involved GPER1 interaction with the non-receptor tyrosine kinase c-Src, which activated the nuclear factor kappa B (NF-?B) pathway. The silencing of GPER1, c-Src or NF-?B p65 subunit blocked E2- or G1-induced SK-Br-3 cell migration and invasion. In cultured MCF-7 cells (ER?+/?+/GPER1+), the silencing of GPER1, while not ER? or ER?, abolished FAK phosphoylation induced by E2 or G1. In parallel, in cultured MDA-MB-231 cells (ER?-/?+/GPER1-), E2 or G1 was unable to stimulate FAK phosphorylation. However, E2 and G1 regained the ability to induce FAK phosphorylation when GPER1 was expressed by the transfection of GPER1 plasmid.
Conclusion: we demonstrated that GPER1, but not ER? or ER?, mediates FAK phosphorylation induced by E2 via c-Src/p65 signaling pathway, which eventually leading to enhanced cell migration and invasion.

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