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Progesterone through Progesterone Receptor-B Inhibits Invasion of Human Breast Cancer Cells by Targeting Cytoplasmic Cyclin D1

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Introduction: Progesterone Receptor (PR) positivity is associated with a good prognosis and better response to breast cancer treatment. Conversely, cyclin D1 (CD1) is retained a marker of poor outcome since it has been associated with breast cancer metastasis in clinical studies.

Material and method: 17-Hydroxyprogesterone (OHPg) was from Sigma-Aldrich. Antibodies and Protein A/GPLUS-Agarose were from Santa Cruz Biotechnology. T47-D, MCF-7 and MDA-MB-231 human breast cancer cells from the American Type Culture Collection; Total real-time RT-PCR assay; Western blotting and immunoprecipitation; Transfections and luciferase assays; Lipid-Mediated Transfection of siRNA Duplexes; Chromatin immunoprecipitation (ChIP) assays and realtime ChIP; Wound-healing assays; Transmigration assays; Cell invasion assay; Phalloidin staining

Results and Discussion: Herein we provide evidences that OHPg through PR-B isoform, reduces motility and invasion of T47-D and MCF-7 breast cancer cells, by targeting the cytoplasmic CD1. Specifically, OHPg reduces CD1 expression through a transcriptional mechanism due to the occupancy of CD1 promoter at a canonical half progesterone responsive element by PR-B. This allows the recruitment of HDAC1 influencing a less permissive chromatin conformation for gene transcription and release of RNA Pol II. CD1 has an active role in the control of cell migration and metastasis through the interaction with key components of focal adhesion such as Paxillin (Pxn). In untreated T47-D and MCF-7 cells a specific co-immunoprecipitation of endogenous cytoplasmic CD1 with Pxn was observed. In untreated T47-D and MCF-7 cells a specific co-immunoprecipitation of endogenous cytoplasmic CD1 with Pxn was detected. Interestingly, OHPg exposure reduced the interaction between these proteins although total Pxn expression was substantially unaffected. Moreover a concomitant reduction of p-Pxn levels was observed and these effects were required for OHPg/PR-B dependent delay in cell invasion, as evidenced by assays carried out with the phoshomimetic mutants of Pxn.

Conclusions: Collectively these findings support the importance of PR-B expression in breast cancer cells behavior, suggesting potentiating of PR-B signaling as a prospective useful strategy to restrict breast tumour cells invasion and metastasis.

Biography:

Francesca De Amicis is an Assistant Professor of Applied Biology, Faculty of Pharmacy and Science of Nutrition and of Health at University of Calabria, Italy. In 1992 he did his Ph.D in Experimental Oncology, Italy. From 2005-2006 he was an Postdoctoral Associate at Breast Center, Baylor College of Medicine, Houston-Texas, USA. His Research Interests include Role of Steroid receptors in tumorogenesis of hormone-dependent tissues.