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# ANGIOCRINE ACTIONS ELICITED BY IGF-I THROUGH THE HIF-1α/GPER/VEGF PATHWAY IN THE BREAST TUMOR MICROENVIRONMENT

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**The G-protein coupled estrogen receptor (GPER) mediates estrogen action in breast cancer cells as well as in breast cancer associated fibroblasts (CAFs), leading to aggressive features of breast disease. In hypoxic conditions, GPER facilitates breast cancer cells adaptation to stressful microenvironment by activating the HIF-1α/VEGF transduction pathway towards new blood vessel formation. Furthermore, the cross-talk between GPER and IGF signalling has been shown to boost relevant biological responses, including breast cancer cell proliferation and migration. Herein, we investigated the angiocrine actions elicited by IGF-I through the cross communication with GPER signalling in breast cancer. First, we performed a bioinformatic analysis of 17 published Affymetrix microarray datasets of 2999 breast cancer patients and of metabric studies performed on 1904 human breast tumor samples, and found that GPER is co-expressed with IGF-IR and with the vessel marker CD34, thus suggesting that both GPER and IGF-IR establish an angiogenic gene signature in breast tumor patients. Next, we used GPER-positive but Estrogen Receptor (ER)-negative SKBR3 breast cancer cells and primary CAFs, which were isolated from breast tumor patients. We performed gene and protein expression studies, promoter analysis and immunofluorescent experiments using pharmacological inhibitors, and we found that IGF-I triggers the activation of the IGF-IR/AKT/ERK transduction pathway toward the up-regulation of HIF-1α, GPER and VEGF expression. Gene silencing strategies were used to demonstrate that both HIF-1α and GPER are required for the up-regulation of VEGF expression. In vitro angiogenesis assays performed in human umbilical vein endothelial cells (HUVECs) showed that both HIF-1α and GPER are involved in endothelial tube formation induced by IGF-I. Altogether, these findings indicate that GPER signaling is engaged by IGF-1 in the breast tumor microenvironment towards new blood vessel formation. Thereafter, targeting GPER/IGF-IR cross-talk may represent a promising combination strategy to block the aberrant angiogenic response in breast cancer.**

### Biography

Ernestina M De Francesco has completed her PhD from the University of Calabria in 2013, where she has been involved in the characterization of estrogen signaling through GPER since 2009. She has joined the University of Manchester (UK) in 2015, where her research activity has been supported by a EU and AIRC (Associazione Italiana per la Ricerca sul Cancro) co-funded fellowship. Currently, she has joined the Translational Medicine Unit at the School of Environment and Life Sciences of the University of Salford (UK). She has published more than 30 papers in reputed journals and has been serving as an Editorial Board Member of repute.

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