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Identification and characterization of annexin A1 as a clinically useful biomarker of responsiveness to PPARG ligand therapy in triple negative breast cancer

Alan Prem Kumar
National University of Singapore, Singapore

The basal-like breast cancer subtype is predominantly estrogen receptor (ER)-, progesterone receptor (PR)-, and C-erb B2 receptor (HER2)-negative, aptly named triple negative breast cancer (TNBC). TNBC lacks defined targeted therapies, and have unique molecular profile, aggressive behavior, distinct patterns of metastasis and, thereby, a poor clinical outcome. Tumors which belong to the basal subtype have a more aggressive clinical behavior when compared to those with a luminal phenotype and that 'basal' status may be an independent prognostic factor. Thus, identifying markers and therapeutic targets for TNBC is of pressing need. Our clinical data established basal and claudin-low subtypes of breast cancer (TNBC types) express significantly higher levels of annexin A1 (ANXA1) with poor survival outcome. Using model cell lines of TNBC, we observed a positive correlation between expression of ANXA1 and nuclear receptor, peroxisome proliferator-activated receptor gamma (PPARG). A similar correlation was also seen in clinical tissues. To establish if these two markers are indeed linked in TNBC, we show that expression of ANXA1 is induced by PPARG activation both *in vitro* and *in vivo* and has a predictive clinical value in determining chemo-sensitivity to PPARG ligands. Mechanistically, we established PPARG-induced ANXA1 protein interacts directly with RIP-1 leading to deubiquitination of RIP-1 thereby activating the death pathway. Since to date there are no published reports on PPARG-ANXA1 axis in RIP-1 induced death machinery in cancer, our study therefore provides new preclinical with mechanistic insight for the suitability of using baseline expression ANXA1 as one inclusion criteria for patient selection in future PPARG chemotherapy trials.

Biography

Alan Prem Kumar earned his Ph.D. from University of North Texas, USA. From his Ph.D. work, he discovered a novel regulatory protein, PyrR for the pyrimidine biosynthetic pathway in Pseudomonas. Because pyrimidine biosynthesis is an essential step in the progression of secondary Pseudomonas infections, PyrR presents an attractive anti-pseudomonal drug target. He then pursued Postdoctoral training in Cancer Research at Sidney Kimmel Cancer Center, California, USA. He was awarded a Postdoctoral Fellowship for his work on the role of nuclear receptors in the transcriptional regulation of human myeloperoxidase, a leukocyte enzyme implicated as causative agent in atherosclerosis and Alzheimer's disease. He relocated back to Singapore to join the Faculty of Medicine, National University of Singapore as an independent Principal Investigator to continue on his expertise on nuclear receptor signaling in cancer biology. His current research focus in the areas of signaling by nuclear receptors and oncogenes in breast tumor cells as well as the development of molecular therapeutics and biomarkers of drug action in breast cancer. His group also focuses on developing new drugs for the treatment of breast cancer. Over the years, he and his group have forged relationships with scientists and oncologists in cancer research and with cancer advocacy groups in Singapore.

csiapk@nus.edu.sg