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Unravelling the mechanism of ERR beta behind its role as a tumor suppressor and contribution of specific miRNAs and co-regulators in breast cancer cell lines

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Our study provides the first evidence that ERRβ, which is a coregulator of ERα also acts as a potential tumour-suppressor molecule in breast cancer. Our current report also provides novel insights into the entire cascade of ERRβ signalling events, which may lead to BCAS2-mediated blockage of the G1/S transition and inhibition of the epithelial to mesenchymal transition through FST-mediated regulation of E-cadherin. Importantly, matrix metalloprotease 7, which is a classical mediator of metastasis and Ecadherin cleavage, was also restricted as a result of ERRβ-mediated FST overexpression. Estrogen receptor-α (ER-α) has been reported to control the expression of genes involved in a wide variety of biological processes, including reproduction, development, and breast tumor progression. The first level of regulation of these genes depends on two types of transcriptional activity of ERα such as ligand independent carried by AF-1 domain and ligand dependent which involve the AF-2 domain of ERα. Second level regulation involves participation of coactivators, Corepressors and chromatin remodeling complexes. We have previously shown that the metastasis-associated protein-1 (MTA1), a component of histone deacetylase and nucleosome remodeling complexes, represses ER-driven transcription by recruiting histone deacetylases to the oestrogen receptor element (ERE)-containing target gene chromatin in breast cancer cells. Using yeast two-hybrid screening to clone MTA1-interacting proteins, we identified a previously uncharacterized molecule, which we named as MTA1-interacting coactivator (MICoA). Because chromatin is a highly dynamic structure and because MTA1 and MICoA could be detected within the same complex, these findings suggest that MTA1 and MICoA might transmodulate functions of each other and any potential deregulation of MTA1 is likely to contribute to the functional inactivation of the ER pathway, presumably by derecruitmenting MICoA from ER target promoter chromatin. Overall, our study also identified six dicer-processed miRNAs which are regulated by BCAS2. Out of six, expression status of four miRNAs mark disease progression; and two new miRNAs although being reported for the first time in breast cancer, require attention of the scientific community due to their highly important targets which are frequently deregulated in breast cancer. Hence our future studies will be directed towards the study of the deregulated signaling pathways affected by the identified miRNAs and thereby validating the role of BCAS2 in microRNA-mediated gene silencing during development of breast cancer. For identification of the Dicer-processed miRNAs regulated by BCAS2, we isolated total RNA after knocking down BCAS2 in MCF-7, and performed microRNA profiling of the samples in Affymetrix miRNA 3.0 platform. Summarized flow chart of the data analyses has been shown in. All samples were processed in triplicates, raw data were collected as Cel files, normalized against quality control and baseline transformed. The overall miRNA expression pattern in the microRNA experiments have been shown in. Both the box-whiskar plot and profile plot interpret that the miRNA intensity values for the knock-down samples has been much constricted to the upper and lower quartiles with the maximum and minimum values restricted compared to control as well indicating the obvious regulation of expression of a significant amount of miRNA population. After normalization, one-way ANNOVA method was applied for derivation of differentially expressed miRNAs with a p-value cut-off of 0.05. These shortlisted miRNAs included miRNAs with insignificant fold changes. Considering the minimum fold change of >2, 6 miRNAs were identified; namely: miR-let-7b, miR-139-3p, miR-4720-5p, miR-486-3p, miR-589 and miR-639. let-7 has been reported to be associated with self renewal of tumor-initiating cells in breast cancer. miR-139-3p has been shown to be upregulated in grade 3 inflammatory breast cancers and downregulated in ER-positive breast cancers. miR-4720-5p is being reported first-time to be expressed in breast cancer cells. Most important implication of this finding remains in the fact that this miRNA has 4 conserved binding sites predicted for ERα as per Target Scan 6.2. miR-486-3p seems to be simultaneously upregulated with miR-139-3p in grade 3 breast cancers in addition to being overexpressed in inflammatory breast carcinoma (IBC). miR-589 has been reported to be downregulated in metastatic breast cancer. miR-639 has not been yet reported to be directly associated with breast cancer; however, its predicted targets from TargetScan and miRanda i.e., *CAT, PTPRJ* and *CYP11B2* have been shown to be involved. Overall, our study resulted in identification of six Dicer-processed miRNAs which are regulated by BCAS2. Out of six, expression status of four miRNAs mark disease progression; and two new miRNAs although being reported for the first time in breast cancer, require attention of the scientific community due to their highly important targets which are frequently deregulated in breast cancer.

Biography

Sandip K Mishra has been an active researcher in the field of epigenetics of breast cancer, since his postdoctoral training in UT MD Anderson Cancer Center, Houston, TX. Before that, his Doctoral thesis was on Molecular Gerontology. He served as a faculty in the Department of Neurosurgery, UT MD Anderson Cancer Center, Houston, TX before moving to a reputed National Institute under Department of Biotechnology, Govt. of India as a senior scientist. Now he is serving as a tenured senir scientist equivalent to Professor and Principal Investigator of Cancer Biology Laboratory. He has published several papers in high impact peer reviewed journals. He is serving on the editorial boards for the Journal of Cancer Science and Research . He is also serving as the Associate Editor of World Journal of Cancer Research , He is an active member of AACR, USA. He has several grants from funding agencies of Govt.of India. Since he started his career in India towards the end of the year 2007, under his guidance one graduate student was already awarded Ph.D. degree. Six more graduate students are working for their Doctoral degrees under his guidance. Besides postdoctoral student, technicians and other project staffs are also working under him. He has been honored with several awards including Amgen Award during his postdoctoral training in UT MDACC. In recent past, his findings was accepted as late breaking abstract in AACR meeting.

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