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Important chromatin modifiers in metastatic breast cancer

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Breast cancer, the most common malignancy in women, was already known to be associated with the steroid hormone estrogen more than a century ago. The discovery of the ER- α provided us not only with a powerful predictive and prognostic marker, but also an efficient target for the treatment of hormone-dependent breast cancer with antiestrogens. Steroid hormones, in particular estrogen and progesterone, play important roles in normal and neoplastic breast development. Alterations in both estrogen signaling and progesterone signaling occur during breast tumorigenesis and breast cancer progression. The transcriptional activity of estrogen receptor- α is modified by coactivators, corepressors, and other chromatin remodeling complexes. It has been demonstrated that the NuRD-70 polypeptide of the nucleosome-remodeling complex is identical to metastatic tumor antigen 1 (MTA1) and that MTA1 physically interacts with HDAC1/2. MTA-1 also interacts with estrogen receptor- α (ER- α) and represses ER transcription by recruiting HDAC to the ERE-containing target gene chromatin in breast cancer cells. The MTA1 gene is shown to correlate well with the metastatic potential of several human cell lines and cancers, including breast cancers. MTA1-overexpressing breast cancer cells exhibit aggressive phenotypes. MTA1s, another family member, is a naturally occurring variant of MTA1 that contains a novel sequence of 33 amino acids with one potential nuclear receptor binding motif, LRILL. MTA1s inhibits ER nuclear signaling by sequestering ER in the cytoplasm but enhances ER cytoplasmic signaling and thus promotes tumor-igenesis. Using a yeast two-hybrid screening to clone MTA1-interacting proteins, we identified a previously uncharacterized molecule, which we named as MTA1-interacting coactivator (MICoA). Our findings suggest that estrogen signaling promotes nuclear translocation of MICoA and that MICoA interacts with MTA1 both in vitro and in vivo. We showed that MICoA is an ER- α coactivator, cooperates with other ER- α coactivators, stimulates ER- α transactivation functions, and associates with the endogenous ER- α and its target gene promoter chromatin. MTA1 also repressed MICoA-mediated stimulation of ERE-mediated transcription in the presence of ER- α and other ER- α variants with naturally occurring mutations, such as D351Y and K303R, and that it interfered with the association of MICoA with the ER- α target gene chromatin. Because chromatin is a highly dynamic structure and since MTA1 and MICoA could be detected within the same complex, these findings suggest that MTA1 and MICoA might transmodulate functions of each other. Deregulation of MTA1 is likely to contribute to the progress of breast cancer through the functional inactivation of the ER- a pathway, presumably by derecruitment of MICoA from ER- α target promoter chromatin. Additionally although studies have shown a role of estrogen receptor-α (ER- α) in the regulation of epithelial-to-mesenchymal transition via MTA3, the role of upstream determinants of ER regulation of MTA3 and the underlying molecular mechanism remains unknown. We have been able to show that MTA3 gene regulation by ER is influenced by dynamic changes in levels of nuclear coregulators.

Biography

Sandip K. Mishra is currently working as a senior Scientist and Principal investigator of Cancer Biology Laboratory, Department of Gene Function and Regulation, Institute of Life Sciences, Bhubaneswar, India. Institute of Life sciences is an autonomous Institute under Department of Biotechnology, Government of India. His main area of research is Epigenetics and Breast Cancer. He did his postdoctoral training at UT MD Anderson Cancer Center (UTMDACC), Houston, TX, USA from 2000 to 2004. During his postdoctoral study on Breast Cancer, he received Amgen Award for his research achievement in UTMDACC. He has several grants from Department of Biotechnology, Govt. of India and Department of Science and Technology, Govt. of India. Before joining his Current Position he was serving as a Faculty in UT MD Anderson Cancer Center, Houston, TX. Currently he is also serving as an Associate Editor in World Journal of Cancer Research which is published by American Scientific Publishers. He is serving as Grant reviewer for different Grant sponsoring agencies of Govt. of India. He has published more than 20 research articles in several top journals including Nature Cell Biology, Nature Structural Biology, Oncogene, Cancer Research, JBC, PLoS ONE etc. He was honored by giving a position like Keynote Speaker in International conference on Cancer research and other International conference. Recently his work was accepted as late breaking abstract category in AACR, 2012.

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