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MicroRNAs induce tamoxifen sensitivity by down-regulation of estrogen receptor alpha signaling in breast cancer

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MicroRNAs (miRNAs) have important regulatory functions in breast cancer tumorigenesis. We previously found that let-7 miRNAs were significantly downregulated in breast cancer tissues, and further demonstrated that these miRNAs target estrogen receptor alpha, resulting in cancer cell apoptosis in breast cancer cell lines. Tamoxifen resistance is a major clinical event in endocrine therapy of breast cancer. Recent studies suggest that overexpression of estrogen receptor (ER)-α36 may be associated with tamoxifen resistance. We hypothesize that let-7 miRNAs family may induce tamoxifen sensitivity by suppressing estrogen receptor (ER)-α36. In this study, we used qRT-PCR to examine expression of let-7 family miRNAs in resistant breast cancer cell lines to tamoxifen as well as expression of estrogen receptor (ER)-α36, a variant of ER-α66, after let-7 miRNA transfection. Immunoblot analysis was employed to check protein expression in FFPE tissue and breast cancer cell lines. Luciferase reporter assay was used to detect direct regulation of let-7 miRNA on ER-α expression. Cell proliferation assay was carried out after transfection of let-7 miRNAs. We found that there was an inverse correlation between the expression of ER-α36 and let-7 family miRNAs (b and i) in the FFPE tissue set. Let-7 miRNA sequences match sequence in the 3' untranslated region (3' UTR) of ER-α36, indicating ER-α36 may be a target of let-7. Co-transfection of let-7 mimics (b and i) with ER-α36 3' UTR luciferase construct decreased the activity of reporter gene. Conversely, let-7 inhibitors (b and i) enhanced the reporter gene activity. Transfection of let-7 mimics (b and i) inhibited both the mRNA and protein levels of ER-α36. On the contrary, transfection of let-7 inhibitors (b and i) enhanced the ER-α36 expression at both mRNA and protein levels in 184A1 cells. The high expression of ER-α36 in tamoxifen resistant MCF7 cells can be inhibited by transfection of let-7 mimics (b and i) and sensitivity toward tamoxifen is enhanced. We conclude that let-7 miRNAs enhance sensitivity of breast cancer cells to tamoxifen through suppression of the expression of ER-α36, suggesting that let-7 could be therapeutic target for breast cancer treatment.

Biography

Dr. Xiao is an Associate Professor and the Director of the Functional Genomics and Proteomics laboratories at the Creighton University School of Medicine, and an internationally recognized expert in the field of genomics and proteomics of cancer and bone disease. Dr. Xiao earns his Ph.D. in molecular computational biology at Chinese Academy of Sciences. He had his postdoctoral research trained in Baylor College of Medicine and UCLA, focusing on pharmacokinetics and biochemistry of non-steroid inflammatory drugs, and cell cycle regulation. He has been regular reviewer or ad hoc reviewer for several medial journals, different funding agency and several journal Editorial Board members.