miR-125b Upregulation Confers Aromatase Inhibitor Resistance and Is a Novel Marker of Poor Prognosis in Breast Cancer

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Increasing evidence indicates miRNAs as important players in oncogenesis. Considering the wide-spread use of aromatase inhibitors (AIs) in endocrine therapy as a first-line treatment for post-menopausal ERα-positive breast cancer patients, identifying deregulated expression levels of miRNAs in association with AI resistance is of utmost importance. To gain further insight into the molecular mechanisms underlying the AI resistance, we performed miRNA microarray experiments using a new model of acquired resistance to letrozole (Res-Let cells), obtained by long-term exposure of aromatase-overexpressing MCF-7 cells (MCF-7aro cells) to letrozole, and a model of acquired anastrozole resistance (Res-Ana cells). Three miRNAs (miR-125b, miR-205 and miR-424) similarly deregulated in both AI-resistant cell lines were then investigated in terms of their functional role in AI resistance development, breast cancer cell aggressiveness and clinical relevance using a cohort of 65 primary breast tumor samples.

We identified the deregulated expression of 33 miRNAs in Res-Let cells and of 18 miRNAs in Res-Ana cells compared to the sensitive MCF-7aro cells. The top-ranked KEGG pathways delineated by both miRNA signatures converged on the AKT pathway, which was found constitutively activated in both AI-resistant cell lines. We report that ectopic overexpression of either miR-125b or miR-205, or the silencing of miR-424 expression in the sensitive MCF-7aro cells were sufficient to confer resistance to letrozole and to anastrozole, to target and to activate the AKT/mTOR pathway; and to increase formation capacity of cancer-initiating-like cells possessing self-renewing properties. Increasing miR-125b expression levels was also sufficient to confer estrogen-independent growth properties to the sensitive MCF-7aro cells. Finally, elevated miR-125b expression levels were a novel marker for poor prognosis in breast cancer, and targeting miR-125b in Res-Let cells overcame letrozole resistance.