The roles of miRNAs in cholesterol-mediated drug resistance in breast cancer

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Introduction: Tamoxifen (TAM) is the "gold standard" and most widely used chemotherapeutic agent for patients with estrogen receptor positive (ER+) breast cancer (BC). It has been reported that 70% of all BC cases are ER+. Recently, ER+ BCs have been shown to accumulate cholesterol to develop resistance to certain drugs[1]. It has emerged that microRNAs (miRNAs) play key roles in several processes including the regulation of cholesterol homeostasis and lipid metabolism[2]. We therefore investigated the effects of the changes in expression of two miRNAs, namely miR-223 and miR-128, on genes involved in cholesterol metabolism and BC drug resistance pathways. Also, to establish their phenotypic effects on BC cell growth and cellular cholesterol levels in response to TAM and a cholesterol depletor (acetyl plumbagin: AP).

Methodology: BC cells were transfected with a mimic to overexpress miR-223 and an inhibitor to knockdown miR-128. Expression of these miRNAs was confirmed in BC cells using RT-qPCR. Following confirmation of overexpression and knockdown of miRNAs, cholesterol staining, and cell viability assays were performed to evaluate the efficacy of miRNA transfection and drug treatment (1 µM TAM + 10 µM AP) in reducing cholesterol content and cell proliferation within BC cells.

Results: RT-qPCR confirmed the significant overexpression of miR-223 (fold change of 3) in ER+ MCF-7 cells in comparison to the non-transfection control. Similarly, a significant knockdown of miR-128 expression (fold change of -1.7) was confirmed in comparison to the non-transfection control. An overall significant reduction in free cholesterol, cholesteryl esters, and lipid rafts was observed in MCF-7 cells post transfection and treatment compared to relevant negative controls. Transfected and treated MCF-7 cells also showed a reduction in proliferation over time compared to negative controls, suggesting increased sensitivity of these cells to the TAM treatment.

Discussion & Conclusion: The aberrant expression of miR-223 and miR-128 significantly alters lipid metabolism and cholesterol homeostasis as well as cancer drug resistance pathways in BC cells.

References:

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