Integrative analysis of miRNA and gene expression reveals regulatory networks in tamoxifen-resistant breast cancer - DTU Orbit (08/11/2019)

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Tamoxifen is an effective anti-estrogen treatment for patients with estrogen receptor-positive (ER+) breast cancer, however, tamoxifen resistance is frequently observed. To elucidate the underlying molecular mechanisms of tamoxifen resistance, we performed a systematic analysis of miRNA-mediated gene regulation in three clinically-relevant tamoxifen-resistant breast cancer cell lines (TamRs) compared to their parental tamoxifen-sensitive cell line. Alterations in the expression of 131 miRNAs in tamoxifen-resistant vs. parental cell lines were identified, 22 of which were common to all TamRs using both sequencing and LNA-based quantitative PCR technologies. Although the target genes affected by the altered miRNA in the three TamRs differed, good agreement in terms of affected molecular pathways was observed. Moreover, we found evidence of miRNA-mediated regulation of ESR1, PGR1, FOXM1 and 14-3-3 family genes. Integrating the inferred miRNA-target relationships, we investigated the functional importance of 2 central genes, SNAI2 and FYN, which showed increased expression in TamR cells, while their corresponding regulatory miRNA were downregulated. Using specific chemical inhibitors and siRNA-mediated gene knockdown, we showed that both SNAI2 and FYN significantly affect the growth of TamR cell lines. Finally, we show that a combination of 2 miRNAs (miR-190b and miR-516a-5p) exhibiting altered expression in TamR cell lines were predictive of treatment outcome in a cohort of ER+ breast cancer patients receiving adjuvant tamoxifen mono-therapy. Our results provide new insight into the molecular mechanisms of tamoxifen resistance and may form the basis for future medical intervention for the large number of women with tamoxifen-resistant ER+ breast cancer.

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