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Opinion Article

Endocrine Therapy Resistance in Breast Cancer: The Emerging Role of MicroRNAs

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Opinion

Despite the effectiveness of surgery and adjuvant treatments in Breast Cancer (BC), questions concerning over- and under-treatment persist; over-treatment can lead to temporary or chronic side effects, lowering the quality of life of patients, on the other hand, under-treatment can cause recurrence with potential life-threatening consequences [1]. We know that endocrine therapy reduces the five-year recurrence rate of Estrogen-Receptor (ER) positive BC by about 50%, however, patients with identical prognostic factors may undergo to substantially different clinical course and treatment response. Endocrine therapy resistance can either exist from the beginning - de novo or intrinsic – or develop during the treatment-acquired [2, 3].

Currently resistance to therapy as well as over- and under-treatment are difficult to predict, especially acquired resistance that becomes evident only when clinically overt. While many new biomarkers have been described over the years, only few have been promoted from the laboratories to the clinic. MicroRNAs (miRNAs) are non-coding single-stranded RNAs about 22 nucleotides long. They regulate gene expression, most often leading to gene silencing by post-transcriptional repression or suppression of mRNA [4]. Despite its recent discover, lots of evidence is implying miRNAs may play a potential role as a both predictive and prognostic biomarker.

Biological activity of estrogens is mediated by ERs, which start transcription of specific genes containing estrogen response element whenever activated by cognate ligands. Endocrine treatment for BC works with a dual strategy by blocking the estrogen action at receptorial level (tamoxifen) or by inhibition of peripheral estrogen synthesis (aromatase inhibitors). Tamoxifen is a selective ER modulator: it may function as an agonist or antagonist depending on target tissue, recruiting either coactivators or corepressors to estrogen transcriptional pathway. Tamoxifen holds antagonistic effects in breast tissue, thus preventing BC development, and cytotoxic effects on BC cells, it exhibits agonistic effects on uterine tissue, increasing the risk of endometrial hyperplasia [5, 6].

Tamoxifen is oxidized by the liver involving various enzymes including cytochrome P450 2D6 into active metabolites: 4-hydroxy-N-desmethyl tamoxifen (endoxifen) and 4-hydroxytamoxifen (4-OHT). These two metabolites undergo phase II conjugation reactions and find their way into cancer cells. 4-OHT prevents estrogen from binding to ERs, and consequently proliferation and cell growth. Levels of estrogen have been correlated to 4-OHT serum concentration. The level of concentration correlates with inter-individual differences in polymorphic metabolic enzymes of tamoxifen pathway that may lead to a potential variation in drug efficacy. Serum concentration is influenced also by age [7, 8].

In 30% of patients, endocrine treatment fails due to tamoxifen resistance. The mechanisms of resistance may involve changes in the activity of the enzymes that metabolize the drug, progressive loss of ER expression, altered balance in coregulatory enzymes, in specific miRNAs expression, or activation of alternative signal transduction pathways that can promote tumor growth anyway [9]. MiRNAs are complementary completely or partially to one or more mRNA molecules, and their main function is to post-transcriptionally down-regulate gene expression by binding or cleaving its target. A single miRNA can potentially target up to 200mRNAs, and the same mRNA can be targeted by different miRNAs. The link between miRNAs and major cellular functions-i.e. development, differentiation, metabolism, motility, proliferation and survival – as well as cancer onset has been vastly demonstrated, since miRNA-encoding genes have been shown to locate at genomic regions allegedly associated with cancer suppression or promotion [10,11].

In BC several miRNAs are aberrantly expressed, comparing malignant tissue to normal tissue. For example miR-21, which results over-expressed in BC, correlates with advanced stage, lymph-node metastases, and poor prognosis, while cell growth, migration and proliferation result inhibited when miR-21 is knocked down. Another well-studied miRNA cluster, miR-17-92, has been implicated in BC promoting tumor cell migration and invasion. MiR-18a and -18b have been shown to specifically target ER, and to be associated with features of basal-like BC, showing additionally enhanced expression in triple-negative tumors compared to luminal As [12,13].

The detection of miRNA in the circulation, either bound to proteins or lipids, inside apoptotic cells, or as part of exosomes suggests the presence of circulating miRNA also in BC patients. In a cohort of 89 BC patients, elevated levels of circulating miR-10b, -155 and -34 have been found in cell-free serum samples. The differences in serum concentration of these miRNAs can even be used to distinguish BC patients from healthy controls, as well as metastatic disease from non-metastatic, and advanced disease from early [14].

All these findings increase the potential for using miRNAs as biomarkers for monitoring BC development and maybe also therapy response. In fact exosomes originating from drug-resistant BC cells have been shown to mediate resistance and drug efflux through exosomal shuttle-miRNAs. In a recent study of tamoxifen-resistant MCF-7 cells, exosomes released from resistant cells have been shown to be able to enter into tamoxifen-sensitive cells and release miR-221 -222, which reduced the expression of p27 and ER in these cells, thus decreasing their sensitivity to endocrine treatment [15].

Some other miRNAs seem to be implied in tamoxifen-resistance too, such as miR-342-5p, which is differentially expressed

in tamoxifen-sensitive versus –resistant cells: its expression in fact results suppressed in tamoxifen-resistant cells while its inhibitor could promote resistance in tamoxifen-sensitive cells. In conclusion, miRNAs are certainly promising biomarkers that could be used to guide ER+BC therapy. It would be interesting to include a combined miRNA profiling of BC patients in future clinical trials with long-term follow-up.

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