Epigenetic Unfolds the Resistance of Endocrine Therapy in Breast Cancer.

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Breast cancer is characteristically a hormone-dependent tumor, and the chances of incidence and proliferation of breast cancer increases with exposure to estrogen. The historical report of treating breast cancer by removing the ovaries established the estrogen-dependent nature of breast cancer. In the last decade treatment of advanced breast cancer has seen a shift from adjuvant tamoxifen to adjuvant aromatase inhibitors in hormone receptor-positive breast cancer. Hormone therapy as a form of systemic therapy has the advantage of reaching cancer cells almost anywhere in the body has gained attention because it can be used to target any kind of cancer cells. It's mostly choice of therapy for women with hormone receptor-positive (ER-positive and/or PR-positive) breast cancers, however with limitations of use in the treatment in women whose tumors are hormone receptor-negative (both ER- and PR-negative). In practice of treatment of breast cancer, drugs called as endocrine therapy are available as option for treating physicians, which includes aromatase inhibitors and others. Gonadotropin-releasing hormone reduces estrogen biosynthesis, the selective estrogen receptor modulators. Patients with ER-positive breast cancer have been beneficial with these drugs with significant improvements in survival outcomes. Like other therapies endocrine therapy also has limitation, where about 20% of patients with early-stage disease experience relapse. Particularly patients with metastatic disease do not show any improvement in the disease condition. It is believed that endocrine therapy resistance in cancer therapy is associated with molecular pathways that promote ligand-independent activation of ER and tumor growth. Some known factors attributing to the resistance of endocrine therapy are mutation in ER-alpha, PI3K/Akt/mTOR, CDK4/6, and epigenetic

regulation. Preclinical studies have confirmed that epigenetic silencing of estrogen receptor and deregulation of growth factor receptor–pathway components play an important role in the development of endocrine resistance. Mutations in genes that regulate histone and DNA modification have also been reported. Continuous efforts are being made to identity DNA methylation signatures that could be prognostic and/or predictive markers in breast cancer and influence in the therapy.

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