

Reversing Hormone Therapy Resistance: A Novel Era of Epigenetic Therapy in Breast and Prostate Cancers

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Editorial

In breast and prostate cancers, hormones mediate the initiation and progression of the disease. These cancers depend on specific steroid hormone receptors, such as estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR). Hormone therapy has become a standard method of treatment for receptor-positive breast and prostate cancers. Despite the fact that most patients initially respond to hormone therapy, with the suppression of tumour growth, resistance develops in a subset of early-stage patients and almost all patients in advanced stages. Furthermore, patients with hormone receptor-positive, ligand-dependent; receptor-positive, ligand-independent; or receptor-negative, ligand-independent are primarily resistant to hormone therapies. Thus, it is essential to understand the mechanism behind the resistance and develop ways to switch from hormone resistance to susceptibility.

The epigenetic modification has emerged as a major contributor to the development of hormone resistance in breast and prostate cancers. Epigenetic regulation of gene expression involves DNA methylation, post-translational modification of nucleosome histones, and miRNAs. In breast cancer, methylation of CpG islands within the promoter of the gene encoding ER- α is one of the main causes of the loss of ER expression in ER-negative breast cancer cells. The epigenetic silencing of ER expression is important for the development of hormone therapy resistance. Currently, several preclinical studies are exploring the epigenetic therapy in the expression of ER using HDAC and DNMT inhibitors. In phase I/II trial, a combination of HDAC inhibitor (panobinostat) and DNMT inhibitor (decitabine) can reactivate ER expression in the tumor of patients with triple negative breast cancer [1]. If ER is reactivated in these cancer patients during 5 days of treatment, they further received tamoxifen to decrease the growth of tumours. A phase II study of vorinostat, an HDAC inhibitor, in combination with tamoxifen and a PD-1 inhibitor was performed in breast cancer patients with resistance to hormone therapy. This trial indicated that the combination of HDAC inhibitor and tamoxifen is well tolerated and exhibits promising method in reversing hormone resistance [2,3]. In phase II trial, combining entinostat with exemestane reduced the risk of disease progression by 27% in postmenopausal patients with ER-positive advanced breast cancer [4]. In prostate cancer, AR pathway signaling is also regulated by CpG methylation and histone acetylation [5]. Inhibition of DNA methylation reversed hormone resistance in both AR positive (LNCaP-HR and 22RV1-HR) and negative cell lines (PC-3) [6]. In phase II trial of Azacitidine, a hypomethylating agent, Sonpavde et al. demonstrated promising effects on PSA kinetics in 36 chemo-naïve patients with progressive disease [7].

Recent studies have still focused on the mechanism by which global epigenetics control ER and AR activity in the context of hormone resistance in breast and prostate cancers. Stone et al showed that DNA hyper methylation which occurs predominantly at estrogen-responsive enhancer but not promoter regions is a crucial determinant of hormone response and associated with hormone resistance in breast cancer [8]. In addition, 5-hmC was suggested as an important epigenetic marker for regulation of the hormone activity via modulating FOXA1 binding. Global 5-hmC modification is controlled by miR-29, a crucial epigenetic regulator that suppresses TET2 in prostate cancer progression [9]. This study proposed novel epigenetic approaches using non-coding RNAs for the treatment of advanced prostate cancer.

Future research is concentrating on reversion of hormone resistance using epigenetic inhibitors. The combination of epigenetic therapy or miRNA/antimiRNA-based therapy with existing hormone therapy in breast and prostate cancers is a current interest. A number of other approaches are being used to identify the subsets of patients most likely to benefit from these novel inhibitors. Efforts should be directed to find biological markers and epigenetic gene signatures that could predict the efficacy of a specific inhibitor. Next-generation sequencing is opening approaches for detection of gene alterations that drive resistance to hormone therapy leading to promote personalized medicine in management and treatment of hormone resistance in breast and prostate cancers. Furthermore, epigenetic markers and gene signatures should be applied to future clinical trials to select prospective patients.

References

1. Re-expression of ER in Triple Negative Breast Cancers.
2. Munster Thum KT, Thomas S, Raha P, Lacey M, et al. (2011) A phase II study of the histone deacetylase inhibitor vorinostat combined with tamoxifen for the treatment of patients with hormone therapy-resistant breast cancer. *Br J Cancer* 104: 1828-35.
3. Reversing Hormone Therapy Resistance With Epigenetic-Immune Modification.
4. Yardley, Ismail-Khan RR, Melichar B, Lichinitser M, Munster PN, et al. (2013) Randomized phase II, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. *J Clin Oncol* 31: 2128-2135.
5. Nakayama, Watanabe M, Suzuki H, Toyota M, Sekita N, et al. (2000) Epigenetic regulation of androgen receptor gene expression in human prostate cancers. *Lab Invest* 80: 1789-96.
6. Chen M.F, Chen WC, Chang YJ, Wu CF, Wu CT (2010) Role of DNA methyltransferase 1 in hormone-resistant prostate cancer. *J Mol Med (Berl)* 88: 953-62.
7. Sonpavde G, Aparicio AM, Zhan F, North B, Delaune R, et al. (2011) Azacitidine favorably modulates PSA kinetics correlating with plasma DNALINE-1 hypomethylation in men with chemo-naïve castration-resistant prostate cancer. *Urol Oncol* 29: 682-689.
8. Stone A, Zotenko E, Locke WJ, Korb D, Millar EK, et al. (2015) DNA methylation of oestrogen-regulated enhancers defines endocrine sensitivity in breast cancer. *Nat Commun* 6: 7758.
9. Takayama K, Misawa A, Suzuki T, Takagi K, Hayashizaki Y, et al. (2015) TET2 repression by androgen hormone regulates global hydroxymethylation status and prostate cancer progression. *Nat Commun* 6: 8219.

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