Ngai, Adv Genet Eng Biotechnol 2012, 1:1
http://dx.doi.org/10.4172/2324-9021.1000e104

Advances in Genetic Engineering & Biotechnology

Editorial

A SCITECHNOL JOURNAL

Epigenetics Interplay between DNA Methylation and Histone Modifications in Breast Cancer

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Breast cancer is the most common cancer among the women worldwide [1]. It accounts for 23% of total cancer cases and 14% of the cancer deaths [2]. Breast cancer is a heterogeneous disease that results from the genetic and epigenetic events, including activation of oncogenes and inactivation of tumor suppressor genes [3,4].

Epigenetics refer to heritable patterns of gene expression that do not result from the changes in the DNA sequence [5]. These involve DNA methylation and histone modifications [6]. Epigenetic silencing through DNA methylation leads to aberrant silencing of normal tumor suppressor genes and causes cancer [7]. In breast cancer studies, it was reported that the genes with putative role in breast cancer undergo hypermethylation, such as p16, CCND2, CDH1, BRCA1, ER and RARβ2 [8,9]. Although DNA methylation controls the gene expression, however, it alone is insufficient to lead to gene silencing [5]. Histone modifications act to stabilize the inactive state of the chromatin and repress the gene expression [10]. However, it is still controversial on what to trigger the initiation of the silencing event. Some experiments demonstrated that DNA methylation lead to histone modifications [11-14] whereas the others show the contradictory evidence [15].

It was reported that DNA methylation and histone deacetylation are partially responsible for the gene silencing of mapsin, which is a tumor suppressor gene in breast cancer cells [16]. Seven other genes which have putative roles in breast cancer development or progression are RARβ2, CDH1, ER, BRCA1, CCND2, p16 and TWIST. These genes were reported to be commonly methylated in breast cancer, leading to down-regulation of expression [4]. Therefore, the re-activation of the tumor suppressor gene could potentially offer a promising new target as a therapeutic option in breast cancer [16].

DNA demethylating agents and the inhibitors of histone deacetylase were shown to be able to re-express the silenced gene [17,18]. He et al. reported that 5-azacytidine (DNA demethylating agent) was able to reactivate the silenced lacZ in a dosage-dependent manner [18]. Ou et al. reported that Trichostatin A (Histone deacetylase inhibitor) was able induce histone acetylation, DNA demethylation and expression of the methylated E-cadherin and RARβ2 genes in human bladder cancer T24 and breast cancer MDA-MB231 cells [17].

Since epigenetic changes are reversible, the demethylating agent and the inhibitor of histone deacetylase could potentially de-repress the silenced tumor suppressor genes, reduce the migration rates of breast cancer cell lines and restore their normal function [5]. The therapeutic application of the epigenetic drugs provides new and effective options for breast cancer patients [5]. More studies need to be done to identify the relation of tumor suppressor genes with the tumor grades and the metastasis status and to identify the precise epigenetic molecular events in tumorigenesis. It is hoped that once the mechanism of epigenetics in tumor suppressor genes of breast cancer has been identified, the gene silencing can be overcome and subsequently lead to great promise for further progress in the field of diagnosis, prognosis and therapy of breast cancer ("Epigenetic therapy")[19].

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Received: July 20, 2012 **Accepted:** July 23, 2012 **Published:** July 28, 2012

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