Tissue specific DNA methylation in normal human breast epithelium and in breast cancer

Abstract:

Cancer is a heterogeneous and tissue-specific disease. Thus, the tissue of origin reflects on the natural history of the disease and dictates the therapeutic approach. It is suggested that tissue differentiation, mediated mostly by epigenetic modifications, could guide tissue-specific susceptibility and protective mechanisms against cancer.

Here we studied breast specific methylation in purified normal epithelium and its reflection in breast cancers. We established genome wide methylation profiles of various normal epithelial tissues and identified 110 genes that were differentially methylated in normal breast epithelium. A number of these genes also showed methylation alterations in breast cancers. We elaborated on one of them, TRIM29 (ATDC), and showed that its promoter was hypo-methylated in normal breast epithelium and heavily methylated in other normal epithelial tissues. Moreover, in breast carcinomas methylation increased and expression decreased whereas the reverse was noted for multiple other carcinomas. Interestingly, TRIM29 regulation in breast tumors clustered according to the PAM50 classification. Thus, it was repressed in the estrogen receptor positive tumors, particularly in the more proliferative luminal B subtype. This goes in line with previous reports indicating tumor suppressive activity of TRIM29 in estrogen receptor positive luminal breast cells in contrast to oncogenic function in pancreatic and lung cancers.

Overall, these findings emphasize the linkage between breast specific epigenetic regulation and tissue specificity of cancer.