The Reactivation of X-linked Tumor Suppressor Gene FOXP3 by Anisomycin and Xist Small Interfering RNA in Breast Cancer Cells

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The FOXP3 gene on the X-chromosome is responsible for the development and function of regulatory T cells. Our previous studies found that FOXP3 also behaves as an X-linked tumor suppressor identified in breast cancer. This fact was proven by the discovery that 1. FOXP3 is inactivated in most of breast cancer tissues; 2. it can inhibit breast tumor growth. This study investigates the mechanisms of FOXP3 inactivation and develops the reactivation strategy of FOXP3 gene in breast cancer cells. By using pyrosequencing, I identified a hypermethylation site at the 5' CpG island of the FOXP3 promoter in breast cancer cells. Surprisingly, a significant increase of methylation in the CpG island strongly correlates to a reduction of FOXP3 expression in breast cancer cells; it does not, however, share similar associations with the T-regulatory cell specific demethylated region (TSDR). In contrast, both the CpG island and TSDR were nearly 100% methylated in Jurkat T cells. Thus, the 5' CpG island appears to be a critical methylation site which may involve epigenetic regulation during the inactivation of FOXP3 in breast cancer cells. In particular, I demonstrated that anisomycin, an anticancer drug, can prompt FOXP3 expression by decreasing DNA methylation of FOXP3. Notably, a non-coding Xist small interfering RNA (siRNA) remarkably enhances anisomycin-induced FOXP3 expression. My data suggested that FOXP3 inactivation may be caused by DNA methylation; essentially, FOXP3 inactivation can be reactivated by anisomycin with Xist siRNA, suggesting a novel therapeutic strategy for breast cancer patients with FOXP3 defects.

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