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Effect of TPA and HTLV-1 Tax on BRCA-1 and ERE Controlled Genes Expression

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Abstract : BRCA-1 is a multifunctional tumor suppressor, whose expression is activated by the estrogen (E2)-liganded ERα receptor. The activated ERα is a transcriptional factor which activates various genes either by direct binding to the DNA at E2-responsive elements (EREs) and indirectly associated with a range of alternative non-ERE elements. Interference with BRCA-1 expression and/or functions leads to high risk of breast or/and ovarian cancer. Our lab investigated the involvement of Human T-cell leukemia Virus Type 1 (HTLV-1) in breast cancer, since HTLV-1 Tax was found to strongly inhibit BRCA-1 expression. In addition, long exposure of 12-O-tetradecanoylphorbol-13-acetate (TPA), which is one of the stress-inducing agents activated the HTLV-1 promoter. So here the involvement of TPA in breast cancer had been examined by testing the effect of TPA on BRCA-1 and ERE expression. The results showed that TPA activated both BRCA-1 and ERE expression. In the 12 hours TPA activated the tow promoters more than others time, and after 24 hours the level of the tow promoters was decreased. Tax inhibited BRCA-1 expression but did not succeed to inhibit the effect of TPA. Then the activation of the two promoters was not through ERα pathway because TPA had no effect on ERα binding to the two promoters of the BRCA-1 and ERE. Also, the activation was not via nuclear factor kappa B (NF-κB) pathway because when the inhibitory of NF-κB had been added to the TPA, it still activated the tow promoters. However, it seems that 53BP1 may be involved in TPA activation of these promoters because ectopic high expression of 53BP1 significantly reduced the TPA activity. In addition, in the presence of Bisindolylmaleimide-I (BI)- the inhibitor of Protein Kinase C (PKC)- there was no activation for the two promoters, so the PKC is agonized BRCA-1 and ERE activation.

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