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The Role of Coactivators and Corepressors in the Induction of RARβ□ Gene in Human Colon Cancer Cells

Hyo-Jin Kang* and Mi-Ock Lee

Department of Bioscience and Biotechnology, Institute of Bioscience, Sejong University, Seoul, KOREA

We previously reported that retinoic acid (RA) insensitivity of RARβ induction is a general feature of human colon cancer cells. In the present investigation, we analyzed potential transcriptional defects associated with the expression of RARβ □gene in colon cancer cells. Transfection of reporter constructs containing RARβ gene promoter as well as truncated fragments of the promoter showed a significant induction of the reporter activity by RA treatment in RA-sensitive HCT-15 cells, but not in RA-resistant DLD-1 cells. The results suggested that the transcriptional defect of RARβ expression may not be due to presence of specific *cis*-element in RARβ promoter. Next we examined whether coactivators and corepressors of nuclear receptors were involved in the RA sensitivity in the colon cancer cells. Transfection of coactivators such as CREB binding protein (CBP) and p300 up-regulated the retinoic acid responsive element present in RARβ promoter (βRARE) in DLD-1 up to the level in HCT-15, while co-expression of the nuclear receptor corepressor (NCoR) suppressed the βRARE activity in HCT-15. Consistently, the expression level of CBP protein was higher in HCT-15, while that of NCoR and Sin3A was higher in DLD-1. Treatment with a histone deacetylase inhibitor, TSA, increased both basal and RA induced βRARE activity in DLD-1, indicating that histone deacetylase is involved in the regulation of RARβ gene expression. Taken all together, our results showed that differential function of coactivators and corepressors may determine the level of RARβ induction that may mediate the retinoid action in colon cancer cells.