ABSTRACT

Transcriptional repression imparted by nuclear hormone receptor co-repressor (N-CoR) is known to play key role in cell growth control mechanism and differentiation. The misfolded conformation dependent loss of N-CoR is linked to abnormal growth as well as transformation of tumour cells in various leukemia and solid tumors. The growth control mechanism of N-CoR relies on its localization to the nuclear domains known as PODs (PML oncogenic domains) which is a frequent target of various oncogenic viruses, including hepatitis virus B (HBV) and human papilloma virus (HPV). HBV and HPV generate highly pathogenic proteins which are directly linked to the transformation of malignant cells in Hepatocellular and cervical cancer. Although, the underlying mechanism of HBV or HPV-induced pathogenesis in hepatocellular and cervical cancer is not known, it is likely that they act through similar mechanism. Thus, it was hypothesized that a functional N-CoR presented in the PODs may actively suppress the oncogenic potential of HBV and HPV by repressing the expression of respective oncogenes and these pathogenic viruses must overcome the N-CoR mediated transcriptional repression by inducing its degradation through misfolding. Therefore, this project was conceived to detect the degradation of N-CoR protein in cancer cells and tissues derived from HCC and cervical cancer through western blotting and ELISA and to determine the subcellular distribution and misfolding of N-CoR through immunohistochemistry. Western blotting assay of N-CoR with the whole cell extracts of various HCC and cervical cancer cells revealed multiple smaller fragments of N-CoR protein which were strongly reactive to anti-N- CoR antibody, suggesting that N-CoR might have been degraded in HCC and cervical cancer cells. ELISA based assay of N-CoR protein with three different anti-N-CoR antibodies revealed reduced level of N-CoR protein across primary HCC and cervical cancer tissues. Next, to test whether N-CoR loss observed in HCC and cervical cancer cells was due to protein misfolding, the subcellular distribution of

endogenous N-CoR protein in primary HCC and cervical cancer tissues was determined through immunohistochemistry. A significant portion of endogenous N-CoR protein, which is basically a nuclear protein in normal conformation, was found in the cytosol of both HCC and cervical cancer tissues, implying that N-CoR could have undergone misfolding in these cancer tissues. These findings collectively suggest an identical mechanism of post-translational loss of N-CoR in HCC and cervical cancer cells. The misfolded N-CoR identified in this project could serve as protein-based biomarker for HCC and cervical cancer.

Keyword: ***N-CoR, HBV, HPV, Misfolding, PML***