2012 Master Thesis Summary

Analysis of the *Coactivator-associated Arginine Methyltransferase 1* (*CARM1*) as a new target of the *trans*-activator protein Tax of HTLV-1

Kwansei Gakuin University, School of Science and Technology
Department of Bioscience, Ohtani Laboratory, Rahma Fitri Hayati

Human T-cell Leukemia Virus Type 1 (HTLV-1) is a leukemogenic retrovirus, which causes adult T-cell leukemia (ATL). HTLV-1 genome encodes the *trans*-activator protein Tax. Tax is known to promote cell proliferation of virus infected cells by activating various genes involved in cell growth. Previous study found that Tax induced expression of the *Coactivator-associated Arginine Methyltransferase 1 (CARM1)* gene. CARM1 facilitates transcription by methylating arginine residues of histone H3. Indeed, CARM1 was reported to cooperate with Tax to activate HTLV-1 LTR. These observations suggest the possibility that induction of *CARM1* gene expression by Tax may facilitates Tax-mediated cellular gene expression and cell cycle progression. This study is objected to clarify the significance of induction of *CARM1* gene expression in Tax-mediated cell cycle progression and mechanism of *CARM1* activation by Tax.

To examine the biological significance of CARM1 expression in Tax-mediated cell cycle progression, CARM1 expression was knocked down using shRNA against CARM1 (shCARM1). The effects of CARM1 knockdown were analyzed at the level of gene expression and cell cycle progression. One of the shCARM1 (shCARM1-2) suppressed expression of Tax target genes (*CDK6*, *Cyclin D2*). Two of the shCARM1s (shCARM1-2 and shCARM1-3) suppressed Tax-mediated cell cycle progression as examined as E2F activation by reporter assay and cell cycle distribution by FACS analysis. These results suggest the important role of CARM1 in Tax-mediated cell cycle progression.

Search for Tax-responsive elements (NF-κB, CREB, and SRF sites) found multiple NF-κB-like sites in CARM1 1st intron (designated as CARM1 downstream, CARM1-DS). Reporter analysis showed that CARM1-DS was activated by Tax. Knockdown of the NF-κB pathway using shRNA against p65 and p100, two members of NF-κB family responsible for canonical and non-canonical pathway, respectively, suppressed CARM1-DS activation by Tax. These results suggest that CARM1-DS activation by Tax was mediated, at least in part, through the NF-κB pathway. Taken together, these results suggest that Tax-mediated activation of *CARM1* gene through the NF-κB pathway may contribute to Tax-mediated cell proliferation by facilitating Tax-mediated gene expression and cell cycle progression.