RETROVIROLOGY

MEETING ABSTRACT Open Access

Genetic and epigenetic loss of miR-31 activates NIK-dependent NF-κB pathway in Adult T-cell Leukemia

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From 15th International Conference on Human Retroviruses: HTLV and Related Viruses
Leuven and Gembloux, Belgium. 5-8 June 2011

Although crucial roles of microRNA have begun to emerge, detailed studies with ATL patients have not been achieved. Using 40 primary ATL samples and 22 samples of normal CD4+ T-cells, we determined the microRNA signatures of ATL and revealed loss of miR-31, which has recently been reported as a metastasis-associated miRNA. All ATL cases invariably showed undetectable or very low levels of miR-31, clearly implying that miR-31 loss is involved in ATL development.

As a novel miR-31 target gene, we identified NF-κB inducing kinase (NIK) that plays central roles in noncanonical signaling and constitutive activation of NF-κB in various cancers, including ATL. Restoration of miR-31 downregulated the levels of NIK and NF-κB activity, resulting in reduction of malignant phenotypes, containing proliferative index, anti-apoptosis, and chemotaxis in ATL cells. Furthermore, lentivirus-introduced miR-31 could induce strong apoptosis in primary tumor cells freshly isolated from ATL patients, indicating pivotal functions of miR-31 as a tumor suppressor.

Global copy number profiling demonstrated that 21 cases out of 168 (12.5%) have genomic loss of 9p21 containing miR-31 region. Furthermore, expression profiling and ChIP assay showed requirement of overexpression of histone methyltransferase in epigenetic suppression of miR-31 and aberrant NF-κB activation in primary ATL cells. Knockdown of methyltransferase complex restored the miR-31 expression and consequently inhibited NIK-dependent NF-κB cascade. These findings illustrated that genetic and epigenetic abnormalities link to NF-κB activation through the loss of miR-31. Considering aberrant epigenomics associated with cancers, the emerging relationship provides us a conceptual advance in understanding the broad-acting oncogenic signaling.

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Published: 6 June 2011

doi:10.1186/1742-4690-8-S1-A128
Cite this article as: Yamagishi *et al.*: Genetic and epigenetic loss of miR-31 activates NIK-dependent NF-κB pathway in Adult T-cell Leukemia. *Retrovirology* 2011 **8**(Suppl 1):A128.

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