



MEETING ABSTRACT

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# Genetic and epigenetic loss of miR-31 activates NIK-dependent NF- $\kappa$ B pathway in Adult T-cell Leukemia

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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<sup>+</sup> 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- $\kappa$ B inducing kinase (NIK) that plays central roles in non-canonical signaling and constitutive activation of NF- $\kappa$ B in various cancers, including ATL. Restoration of miR-31 downregulated the levels of NIK and NF- $\kappa$ B 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- $\kappa$ B activation in primary ATL cells. Knockdown of methyltransferase complex restored the miR-31 expression and consequently inhibited NIK-dependent NF- $\kappa$ B cascade. These findings illustrated that genetic and epigenetic abnormalities link to NF- $\kappa$ B 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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