別紙様式第４

学　位　論　文　要　旨

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[論文題名]

Degradation of p47 by autophagy contributes to CADM1 overexpression in ATLL cells through the activation of NF-κB

成人Ｔ細胞白血病リンパ腫における p47 発現低下は NF-κB の活性化を介して CADM1 の高発現を誘導する

(Scientific Reports, accepted)

[要　旨]

Adult T-cell leukemia/lymphoma (ATLL) is a refractory hematological malignancy, which is caused by infection with human T-cell leukemia virus type 1 (HTLV-1). In Japan, approximately one million people are infected with the virus, of which up to 5% will develop ATLL after a long infection period. In our previous studies, cell adhesion molecule 1 (CADM1), a member of the immunoglobulin super family, was identified as a specific cell surface marker for ATLL (Blood 2005). High expression of CADM1 has an important role in enhanced invasion of ATLL cells into many organs. In this thesis, I have investigated the mechanisms of overexpression of CADM1 in ATLL. The NF-κB-like binding site in -729 to -680 bp from the transcription start site of the CADM1 promoter was found to be important for CADM1 transcription activation in both HTLV-1-infected and ATLL cell lines. In HTLV-1-infected T cells, CADM1 expression was dependent on HTLV-1-encoded Tax protein through activation of canonical and non-canonical NF-κB pathways; however, in ATLL cells with loss of Tax expression, activated canonical NF-κB pathway enhanced the CADM1 expression. Further, I demonstrated that degradation of p47, N-ethylmaleimide-sensitive factor (NSF) and valosin-containing protein (p97) cofactor for transport vesicle/target membrane fusion is essential for activation of canonical NF-κB through stabilization of NEMO in ATLL cells. I also demonstrated that the mechanism of p47 degradation is primarily dependent on activation of lysosomal/autophagy signaling and autophagy signaling is activated in most of the HTLV-infected and ATLL cells. Therefore, p47 degradation might be a first key molecular event of the HTLV-1 infection to T cells as a connector of two important signaling pathways, NF-κB and autophagy, which may be important for the development of ATLL.

備考　論文要旨は、和文にあっては 2，000 字程度、英文にあっては 1，200 語程度とする。