論文題目

GANP is involved in anti-HIV-1 infectivity response by facilitating the encapsidation of APOBEC3G into virion cores

(GANPはAPOBEC3Gのウイルスコアへの運搬を介してHIV-1感染阻止応答に関与している)

Background and Purpose: Several host proteins are known to affect HIV-1 infectivity by interfering viral replication. APOBEC3G (A3G) catalyzes cytidine deamination of the viral genomic cDNA as a potent anti-HIV-1 host component. Germinal center-associated nuclear protein, GANP, is associated with AID and involved in generation of somatic hypermutation of *immunoglobulin V-region* in B cells. This study addressed whether GANP is associated with A3G in T cells and involved in HIV- 1 infectivity.

Methods: HIV-l viruses were produced by transfection of wild-type (wt) pNL4-3 and ΔVif pNL4-3E-R- expression vectors. To examine the association of GANP with A3G, we used FLAG-tagged GANP and A3G-HA-tagged expression vectors with HIV-1 in the cells. The association of GANP and A3G was further examined inside of virions (encapsidation) produced from the transfectants. Association of GANP with *HIV-1 genome (g)* RNA was examined by virion chromatin immunoprecipitation assay. The effect of GANP upon A3G in generation of G to A mutation was determined by sequencing and the change of viral infectivity was measured with HIV-1 vector carrying luciferase reporter activity. The effect of GANP in regulation of HIV-l replication was measured by the p24 capsid production after siRNA treatment.

Results: Both GANP and A3G are expressed at high levels in human T cell line H9 and also up-regulated in peripheral blood $CD4^+$ T cells after stimulation with anti-CD3/CD28 beads with IL-2 *in vitro*. GANP physically interacts with A3G at the cytoplasm in transfectants and both proteins appear in HIV-1 virions via capsid- and nucleocapsid-dependent manners, respectively. GANP enhances the A3G encapsidation from viral matrix into virion cores where *HIV-1* gRNA exists as the complex with A3G and various cellular RNAs including *7SL* RNA. Consequently, GANP augments the effect of A3G in generation of G to A mutation in the proviral genome from HIV-1 transfectants and impaired their infectivity. This effect was reciprocally proved by GANP-knockdown experiments. H9 T cell line infected with *wt* HIV-l (produced in GANP-knockdown 293T cells) represents the higher infectivity compared with siControl-treated H9 cells. GANP is associated with A3G to enhance its anti-HIV- 1 activity by generating mutations of the viral genome, impairing the HIV- 1 replication.

Conclusions: GANP is a novel host factor that associates with A3G and regulates its anti-retroviral activity in human $CD4^+$T cells.