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藤井節郎記念医科学センター1F 藤井節郎記念ホール

Weak protein interactions involved in
retroviral trafficking in cells

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Some retroviruses require the Endosomal Sorting Complex Required for Transport (ESCRT) pathway for trafficking inside the cell. They rely on ubiquitin (Ub) signaling to recruit the proper ESCRT complex. HIV-1 Gag-polyprotein recruits Tsg101, a component of the ESCRT-I, through its target sequence PTAP. HIV-1 Gag is ubiquitinated and Tsg101 is also known to bind Ub. This Ub involvement can enhance Tsg101 interaction with HIV-1 Gag. How these two components in signaling between HIV-1 Gag and ESCRT determine its trafficking in the host cell is unclear. Using solution NMR we recently showed that Tsg101 can also recognize Di-Ub, further complicating the regulation mechanism. The interaction to the second Ub monomer is quite weak and could only be observed using NMR paramagnetic relaxation enhancement (PRE) or lanthanide induced pseudo contact shifts (PCS). We indicated that the proximal Ub monomer can occupy two different binding sites on Tsg101. We additionally showed that binding to each of these sites had a distinct outcome in the viral trafficking phenotypes. To inhibit Tsg101 interaction with Ub we identified a family of compounds known as prazole. We showed that the prazole binds Tsg101 covalently in the distal Ub binding site. This reduces Tsg101 co-localization with HIV-1 Gag at the plasma membrane, therefore blocking viral particle formation. It also enhances poly-ubiquitinylation of HIV-1 Gag and promotes its degradation. The E3 Ub conjugating enzyme that is thought to be involved in HIV-1 Gag processing is Nedd4. We tested its HECT domain interaction with Tsg101 and found we could only observe their interaction using PRE or PCS. We concluded that their interaction is encounter like with a very weak orientational preference. Mutational studies on the HECT domain confirmed that the encounter sites along the interface between its N- and C-lobe to be important for viral particle production and release.

教職員、大学院生、学部学生等、
興味を持つ全ての方のご来聴を歓迎致します

お問合せ先： 先端酵素学研究所セミナー運営委員会

(第 49 回担当：分子生命科学分野・齋尾 智英, 松崎元紀)

主催：徳島大学先端酵素学研究所 共催：文部科学省共同利用・共同研究拠点事業

