Identification and Characterization of a New Type of Inhibitor against the HIV-1 Nucleocapsid Protein

J. C. You¹, M-J. Kim²

¹The Catholic University of Korea, ²Catholic University of Korea

Purpose

The human immunodeficiency virus type-1 (HIV-1) nucleocapsid protein (NC) is an essential and multifunctional protein involved in multiple stages of the viral life cycle such as reverse transcription, integration of proviral DNA, and especially genome RNA packaging. For this reason, it has been considered as an attractive target for the development of new anti-HIV drugs. Although a number of inhibitors of NC have been reported thus far, the search for NC-specific and functional inhibitors with a good antiviral activity continues.

Methods

To examine antiviral effect and mode of action of A1752, novel small molecule NC inhibitor, we infected MT4 cells with HIV-1/NL4-3 strain and the resulting viral titer was determined using p24 ELISA and reinfection assay. For examination of binding between NC and A1752, SPR assay was applied. To identify phenotype of virion modified by A1752, qRT-PCR, western blot and northern blot assay were performed.

Results

In this study, we report the identification of A1752, a small molecule with inhibitory action against HIV-1 NC, which shows a strong antiviral efficacy and an IC50 around 1 μM. A1752 binds directly to HIV-1 NC, thereby inhibiting specific chaperone functions of NC including Psi RNA dimerization and complementary trans-activation response element (cTAR) DNA destabilization, and it also disrupts the proper Gag processing. Further analysis of the mechanisms of action of A1752 also showed that it generates noninfectious viral particles with defects in uncoating and reverse transcription in the infected cells.

Conclusion

These results demonstrate that A1752 is a specific and functional inhibitor of NC with a novel mode of action and good antiviral efficacy. Thus, this agent provides a new type of anti-HIV NC inhibitor candidate for further drug development.