Rueda et al. Retrovirology 2010, 7(Suppl 1):P163
http://www.retrovirology.com/content/7/S1/P163

RETROVIROLOGY

POSTER PRESENTATION Open Access

Allosteric regulation by non peptidic, low molecular weight compounds of CCR5 coupling to g-proteins and interaction with Gp120 - consequences on inhibition of R5 HIV-1 infection

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From 16th International Symposium on HIV and Emerging Infectious Diseases
Marseille, France. 24-26 March 2010

Background

Low molecular weight CCR5 ligands inhibit R5-tropic HIV-1 entry into cells. They bind to regions of CCR5 separate from the viral envelope gp120 binding site and would act by an allosteric mechanism, *i.e.* by inducing CCR5 conformational changes, which in turn might reduce CCR5 affinity for gp120. Indeed, these compounds block allosterically chemokine (CHK) binding to CCR5. Some of them are inverse agonists for CCR5, and stabilize G-protein uncoupled, inactive CCR5. But, whether all of them are inverse agonists and to what extent inverse agonism (*i.e.* G protein uncoupling) contributes to antiviral activity is unclear.

Methods

Standard protocols reported elsewhere were used. ^{35}S-gp120 from the Bx08 strain was produced using a SFV type vector in BHK cells. Viral progeny with the renilla-luciferase gene was used to infect U87 cells or PBMCs.

Results

The inhibitors Maraviroc (MVC) and TAK779 are weak and full inverse agonists for CCR5, respectively, and stabilize distinct receptor conformations. TAK and MVC promote CHK dissociation from the receptor with an efficiency correlating with their inverse agonist efficacy. However, we found that gp120 is a CCR5 antagonist, so that its dissociation does not depend on CCR5 uncoupling from G-proteins. Kinetic studies showed that gp120 dissociation from CCR5 (k_{off} = 0.59 h^{-1}) is enhanced in the presence of TAK (5.4 h^{-1}), and to a lesser extent by MVC (1.6 h^{-1}). However, in displacement experiments of ^{35}S-gp120 binding, affinities of MVC and TAK for CCR5 are in the same range (IC_{50}~7 *vs* 21 nM), although MVC is 100-fold more potent than TAK for inhibiting HIV infection.

Discussion

Our results imply that gp120 has a lower affinity for TAK- than for MVC-bound CCR5, although TAK has a weaker antiviral activity. Thus, blocking of infection by these compounds does not solely rely on their ability to reduce affinity of CCR5 for gp120.

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Published: 11 May 2010

doi:10.1186/1742-4690-7-S1-P163
Cite this article as: Rueda *et al.*: Allosteric regulation by non peptidic, low molecular weight compounds of CCR5 coupling to g-proteins and interaction with Gp120 - consequences on inhibition of R5 HIV-1 infection. *Retrovirology* 2010 **7**(Suppl 1):P163.

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