The Two Human CXCR4 Isoforms Display Different HIV Receptor Activities: Consequences for the Emergence of X4 Strains

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Résumé

CXCR4 is a chemokine receptor that plays key roles with its specific ligand, CXCL12, in stem cell homing and immune trafficking. It is also used as a coreceptor by some HIV-1 strains (X4 strains), whereas other strains (R5 strains) use an alternative coreceptor, CCR5. X4 strains mainly emerge at late stages of the infection and are linked to disease progression. Two isoforms of this coreceptor have been described in humans, CXCR4-A and CXCR4-B, corresponding to an unspliced and a spliced mRNA, respectively. Here, we show that CXCR4-B, but not CXCR4-A, mediates an efficient HIV-1 X4 entry and productive infection. Yet, the chemotactic activity of CXCL12 on both isoforms was similar. Furthermore, HIV-R5 infection favored CXCR4-B expression over that of CXCR4-A. In vitro infection with an R5 strain increased CXCR4-B : CXCR4-A mRNA ratio in peripheral blood mononuclear cells (PBMC), and this ratio correlated with HIV RNA plasma level in R5-infected individuals. In addition, the presence of the CXCR4-B isoform favored R5 to X4 switch more efficiently than CXCR4-A in vitro. Hence, the predominance of CXCR4-B over CXCR4-A expression in PBMC was linked to the capability of circulating HIV-1 strains to use CXCR4, as determined by genotyping. These data suggest that R5 to X4 switch could be favored by R5 infection-induced overexpression of CXCR4-B. Finally, we achieved a specific siRNA-mediated knockdown of CXCR4-B. This represents a proof of concept for a possible gene therapeutic approach aimed at blocking the HIV coreceptor activity of CXCR4 without knocking down its chemotactic activity.

Mots-Clés: HIV coreceptor, R5 to X4 switch, chemokine receptor

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