Crystal structure of HIV co-receptor CCR5

Human immunodeficiency virus (HIV) has been well known to cause acquired immunodeficiency syndrome (AIDS). The first step of HIV infection is membrane fusion between the virus and the target cell, which is mediated through interactions of the viral envelope glycoprotein gp120 with the receptor CD4 on the cell and also with the co-receptor, either CCR5 or CXCR4. The structure-function relations of the co-receptors remain poorly understood, because both CCR5 and CXCR4 belong to the membrane protein family of G protein-coupled receptors (GPCRs), and structural studies of GPCRs are enormously challenging. The crystal structures of CXCR4 have been determined (*Science*, **2010**, 330: 1066—1071). Funded by MOST, NIH, NSFC and CAS, researchers led by Prof. Wu Beili from Shanghai Institute of Materia Medica, Chinese Academy of Sciences recently solved the crystal structure of CCR5 bound to an anti-HIV drug maraviroc at 2.7 Å resolution. This work has been published in *Science* (**2013**, 341: 1387 1390).

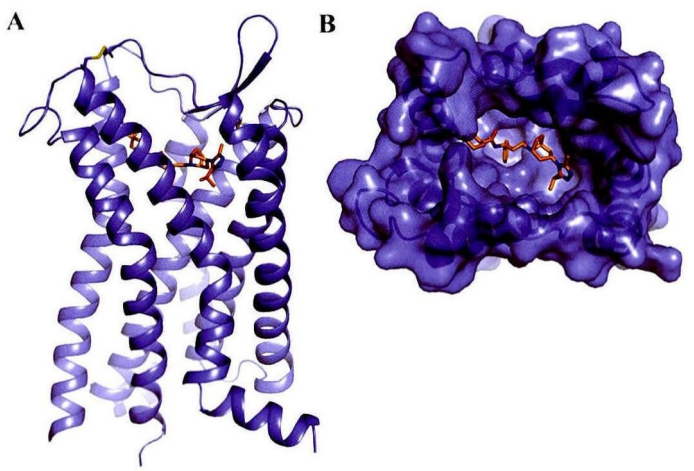

Figure **A** CCR5 maraviroc structure. **B** Top view of CCR5 ligand binding pocket. CCR5 is shown in blue cartoon and surface. Maraviroc is shown in stick.

Previous mutagenesis and pharmacological studies have demonstrated that maraviroc inhibits binding of gp120 to CCR5 in an allosteric mode of action. The CCR5 structure reveals a ligand binding site that is distinct from the proposed major recognition sites for gp120, but potentially overlaps with the receptor activation site. This observation indicates that maraviroc may interfere with the effects of gp120 binding by blocking receptor activation. Maraviroc has been characterized as an inverse agonist of CCR5, suggesting that maraviroc stabilizes CCR5 in an inactive conformation. In the CCR5-maraviroc structure, two conserved class A GPCR residues Trp-248$^{6.48}$ and Tyr-244$^{6.44}$, which are involved in receptor activation, are in conformations similar to those observed in other inactive structures. And maraviroc forms an interaction with Trp-248$^{6.48}$, preventing its activation-related motion. Thus, maraviroc may also reduce gp120 binding in an allosteric inverse agonism manner by stabilizing CCR5 in an inactive conformation. Structural characterization of ligand binding behavior of CCR5, along with knowledge that we gain from the CXCR4 structures, lays a foundation for carrying out next generation drug discovery aimed at inhibiting viral entry of different HIV strains.

HIV can infect a variety of CD4-expressing immune cells by changing its co-receptor specificity. Viruses that use CCR5 for entry are predominant during the early stages of HIV infection, while viruses using CXCR4 emerge in late-stage disease and are related with the progression to AIDS. Comparing the structures of CCR5 and CXCR4, along with models of co-receptor gp120-V3, it is found out that the different characteristics of ligand binding pockets in the two receptors, such as charge distributions and steric hindrances caused by residue substitutions, may be the major determinants of HIV co-receptor selectivity. The structures of both CCR5 and CXCR4 deepen our understanding of the exact molecular details and mechanism of HIV infection, and address specificity issues as well as factors that define viral gp120 binding.