Introduction

The C-X-C chemokine receptor 4 (CXCR4) is a seven transmembrane G protein coupled receptor (GPCR) of stromal cell-derived factor-1 (SDF-1). CXCR4 is expressed widely in immune system and central nervous system. The CXCR4/SDF-1 axis plays important role in multiple physiological processes. The binding of SDF-1 to CXCR4 activates multiple downstream pathways. CXCR4 is discovered to play major roles in stem cell migration and hematopoiesis[1, 2]. As early as in the 1990’s, CXCR4 was identified as the co-receptor for infection of HIV into CD4 T lymphocytes[3]. The HIV virus uses CXCR4 as co-receptor was subsequently designated X4-tropic HIV strain. The natural ligand SDF-1 showed antiviral activity by binding to CXCR4 competitively. Although the binding modes of SDF-1 and viral gp120 to CXCR4 are not disclosed to be identical, SDF-1 does show competitive binding with the virus[4]. This indicates that SDF-1/CXCR4 is a potential target for anti-HIV research. Attribute to the important physiological functions, the knockout of SDF-1 or CXCR4 leads to serious even lethal confusion of the physiology system[5, 6]. A feasible strategy to target CXCR4 for anti-HIV research is development of CXCR4 antagonist since non-functional SDF-1 analogues show antiviral activity.

Numerous studies have been performed to develop successful CXCR4 antagonists which can block the HIV infection through CXCR4. Many drug candidates have been reported to interfere HIV infection by functioning as CXCR4 antagonists[7-9]. Generally, those CXCR4 antagonists can be divided into two categories: peptide CXCR4 antagonist and non-peptide CXCR4 antagonist. The cyclic CVX15 peptide, the T140 peptide, the FC131 peptide and the FC122 peptide are examples of peptide CXCR4 antagonist with anti-HIV activity[10]. The cyclic CVX15 peptide is the modified product from the linear CVX15 peptide. The T140 peptide is derived from polyphemusin II and serves as a scaffold for CXCR4 antagonist design. Based on the identification of the pharmacophore associated with T140, the peptide FC131 was discovered to be a low nanomolar antagonist of CXCR4. Modification of the FC131 leads to the discovery of the FC122 peptide, a more potent CXCR4 antagonist[10]. To stop the virus infection, besides CXCR4, gp160 (gp120 and gp41) and SDF-1 are also effective targets for drug design. The interaction between co-receptor CXCR4 and HIV is mainly an interaction between CXCR4 and viral gp160, especially the V3 region in gp120. The interaction between CXCR4 and the viral gp160 is a complex process. The binding of gp120 is the initiation of virus infection, inducing conformational change of gp41 for co-receptor binding. Gp120 failed to induce CXCR4-G protein interactions in T cells but showed antagonist effect to SDF-1α. The binding affinity of gp120 to CXCR4 was ten times lower than to CD4. So CD4 may plays a role in facilitating the binding to gp120 to CXCR4[11]. Mimicking the viral gp160 results in peptides with anti-HIV activity. F peptide was synthesized corresponding to the residues 414-434 of gp120 of Bru strain of HIV[12].

AMD3100, a bicyclam derivative, is the first promising non-peptide CXCR4 antagonist[7]. Based on the potent anti-HIV activity, AMD3100 had been approved for clinical trial in patients infected with HIV. But AMD3100 was terminated for treatment of HIV infection for the cardiac related side effect[13, 14]. Although AMD3100 was finally proved not suitable for treatment of AIDS, it has been widely applied in stem cell and cancer related research[15, 16].
Following AMD3100, other small molecule CXCR4 antagonists such as ADM070 and AMD3465 have been developed for anti-HIV research\cite{8, 17}. The AMD compounds are representative of non-peptide CXCR4 antagonists. The C-C chemokine receptor 5 (CCR5) is the co-receptor for infection of HIV into macrophage\cite{18}. Similar with CXCR4, CCR5 is also regarded as an important target to inhibit HIV infection. Different from the target of CXCR4, the first CCR5 antagonist, maraviroc, has been approved by FDA for clinical application\cite{19}. The approval of CCR5 antagonist encourages efforts in CXCR4 antagonist development. The development of a successful CXCR4 antagonist is not a plain sailing. It is a long term process and multiple positive factors are involved in this course. Among all the factors, the target itself is the most important one. Five CXCR4 crystal structures together with small molecule antagonist IT1t and cyclic CVX15 peptide were disclosed in 2010\cite{20}. With further understanding of the CXCR4 structure, more precise and useful information is provided. This may greatly accelerate the design of novel CXCR4 antagonist.

Considering the important physiological role, CXCR4 is not suitable for deletion from the human genome. Although CXCR4 modification based gene therapy may be another choice, CXCR4 based gene therapy is far from clinical application. The major consideration is the long term safety. As mentioned above, CXCR4 is involved in many important physiological activities, it is very difficult to thoroughly evaluate the consequences of gene therapy. Therefore, development of CXCR4 antagonist is a more feasible strategy for this target.

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References


