HIV gp41 trimer mimics for vaccines and fusion inhibitors

Wataru Nomura, Chie Hashimoto, Hirokazu Tamamura
Department of Medicinal Chemistry, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (Tokyo, Japan)

Several useful anti-AIDS drugs have been discovered, however, the antibody therapy is still a promising and desirable treatment. To develop effective HIV vaccines and fusion inhibitors, artificial molecules have been synthesized based on HIV-1 envelope proteins such as gp120 and gp41. Gp41 plays a pivotal role in the membrane fusion process of HIV-1 infection, and is divided by the N-terminal helix region (N36) and the C-terminal helix region (C34). In the membrane fusion process, a six-helical bundle structure of gp41 is formed, which consists of a trimeric coiled-coil of N36 surrounded by three strands of C34 in an antiparallel fashion. Thus, it suggests that antibodies which recognize the N36 or C34 trimer might block HIV-1-entry. To construct an N36 trimer mimic, three strands of the N36 peptides were assembled on a C3-symmetric template with three equivalent linkers by thiazolidine ligation for chemoselective coupling of a Cys-containing unprotected N36 peptide with an aldehyde scaffold-containing three arms. Sera produced by immunization of the synthetic N36 trimer antigen showed structural preference in binding to the N36 trimer and higher potent neutralizing activity, compared to sera produced by the N36 monomer immunization. In design of the C34-derived peptides, glycine thioester was fused to the C-terminus of C34 sequence. To form a triple helix corresponding precisely to the gp41 pre-fusion form, the novel C3-symmetric template was designed. This approach used native chemical ligation for chemoselective coupling of unprotected C34REG-thioester with a three-armed cysteine scaffold to produce triC34e. The potency of this C34 trimer mimic as an antigen and as a fusion inhibitor were tested. As an antigen, the trimer induced structural specific antibody as N36 peptides. Moreover, the C34 trimer showed a 100-fold increase of inhibition activity compared to the monomer. Our present results would be useful for HIV vaccine and fusin inhibitor design based on the natural structure of proteins correlated to HIV fusion mechanisms.