Solution structure of a novel T-cell adhesion inhibitor derived from the fragment of ICAM-1 receptor: cyclo(1,8)-Cys-Pro-Arg-Gly-Gly-Ser-Val-Cys

Abstract

This study is aimed at elucidating the structure of a novel T-cell adhesion inhibitor, cyclo(1,8)-CPRGGSVC using one- and two-dimensional 1H NMR and molecular dynamics (MD) simulation. The peptide is derived from the sequence of its parent peptide cIBR (cyclo(1,12)-PenPRGGSVLVTGC), which is a fragment of intercellular adhesion molecule-1 (ICAM-1). Our previous results show that the cyclo(1,8)-CPRGGSVC peptide binds to the LFA-1 I-domain and inhibits heterotypic T-cell adhesion, presumably by blocking the LFA-1/ICAM-1 interactions. The structure of the peptide was determined using NMR and MD simulation in aqueous solution. Our results indicate that the peptide adopts type-I β-turn conformation at the Pro2-Arg3-Gly4-Gly5 (PRGG) sequence. The β-turn structure at the PRGG motif is well conserved in cIBR peptide and ICAM-1 receptor, which suggests the importance of the PRGG motif for the biological activity of cyclo(1,8)-CPRGGSVC peptide. Meanwhile, the Gly5-Ser6-Val7-Cys8-Cys1 (GSVCC) sequence forms a “turn-like” random coil structure that does not belong to any structured motif. Therefore, cyclo(1,8)-CPRGGSVC peptide has only one structured region at the PRGG sequence, which may play an important role in the binding of the peptide to the LFA-1 I-domain. The conserved β-turn conformation of the PRGG motif in ICAM-1, cIBR, and cyclo(1,8)-CPRGGSVC peptides can potentially be used to design peptidomimetics.

Keyword: Autoimmune diseases; b-turn; ICAM-1 LFA-1; T-cell adhesion