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Immunomodulation by peptidomimetics: Targeting CD2-CD58 protein-protein interaction for cell adhesion inhibition

Seetharama Satyanarayanajois, Ameya Gokhale and Veena Taneja
University of Louisiana at Monroe, USA

Costimulatory molecules are targeted for immune intervention in inflammatory and autoimmune diseases. Among the co-stimulatory molecules, CD2-CD58 molecular pairs provide the adhesion between T cell and antigen presenting cell for signaling in the very early stage of immune response. The protein-protein interaction (PPI) between CD2 and CD58 (CD48 in rodents) helps enhance T cell-antigen-presenting cells (APC) adhesion and thus promotes T-cell activation. Studies related to structure of proteins indicated that PPI surfaces have "hot-spots" that are hydrophobic in nature and PPI can be modulated by targeting small molecules or peptides. Our strategy is to use conformationally constrained peptides to inhibit protein-protein interactions in the key regions of the CD2-CD58 interactions. The result of blocking CD2-CD58 interaction will lead to suppression of T-cell activation and is clinically important for the treatment of autoimmune diseases. We have designed cyclic peptides and peptidomimetics from the surface epitopes of CD2 protein to inhibit CD2-CD58/CD48 interaction ultimately resulting in immunomodulation. The cell adhesion inhibition activity of the designed peptides (compound 6 and 7) were studied by cell adhesion assay. Compounds 6 and 7 inhibit the cell adhesion with an IC_{50} value of 6 and 11 nM respectively. Antibody binding inhibition assay indicated that these compounds bind to cells expressing CD58/CD48 proteins. Compounds were evaluated for their ability to modulate the immune response in collagen induced arthritis model (CIA). Results suggested that both the compounds were able to suppress the progression of arthritis in CIA model and were able to suppress T cell response in transgenic animal model.

Biography

Seetharama Satyanarayanajois is an Associate Professor in the Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of Louisiana at Monroe. Jois and obtained his Ph.D. degree in the molecular biophysics unit at the Indian Institute of Science, Bangalore, India. During the past several years, he has worked extensively on the design of peptide/peptidomimetic molecules to target proteins that are important in human diseases using computational and experimental techniques. He is the author and co-author of more than sixty publications. He has edited a special series in Methods in Molecular Biology, Drug Design and Discovery-Methods and Protocols (Humana Press 2011).

jois@ulm.edu