No 18

NMR and Molecular Dynamic Conformational Studies of Two Peptide Analogues of a Myelin Basic Protein Epitope 74-85 Implicated in Multiple Sclerosis

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Detailed ^{1}H chemical shift assignments, 2D ^{1}H-^{1}H NOESY experiments, and conformational properties of two potent linear dodecapeptide analogues of Myelin Basic Protein are reported. The two analogues Gln^{74}-Lys^{75}-Ser^{76}-Gln^{77}-Arg^{78}-Ser^{79}-Gln^{80}-Asp^{81}-Glu^{82}-Asn^{83}-Pro^{84}-Val^{85} (MBP_{74-85}) and Gln^{74}-Lys^{75}-Ser^{76}-Gln^{77}-Arg^{78}-Ser^{79}-Gln^{80}-Ala^{81}-Glu^{82}-Asn^{83}-Pro^{84}-Val^{85} (Ala^{81} MBP_{74-85}), which induce and inhibit respectively Experimental Autoimmune Encephalomyelitis [EAE, the animal model of Multiple Sclerosis (MS)], differ only in the aminoacid residue at position 81 (Asp or Ala). 2D ^{1}H-^{1}H NOESY experiments in DMSO indicate a number of significant inter-residue NOEs, such as strong NOE connectivities between βVal^{85}-γGln^{74} in MBP_{74-85} and βPro^{84}-γGln^{74} in Ala^{81} MBP_{74-85}. Restricted molecular dynamics based on NOE constrains indicate the close proximity of Lys^{75}/Arg^{78}/Asp^{81} side chain observed in agonist MBP_{74-85} but not in antagonist Ala^{81} MBP_{74-85}, which may account for the triggering of the disease. Conformation differences between DMSO and H_2O solution will be discussed in detail.

No19

Crystal Structures of Non-Canonical Low and High Affinity Peptide Complexes with MHC Class I: A Novel Use of Alternative Anchors

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Peptides bind MHC class I molecules by anchoring hydrophobic side chains into specificity pockets in the peptide binding groove. Peptides that do not contain these canonical anchor residues normally have low affinity that results in loss of stable complex formation and loss of immunogenicity. We recently determined the crystal structure at 1.6Å resolution of an immunogenic, low affinity, MUC1 peptide bound to H-2K^b, where binding is achieved despite small non-canonical residues in the C and F anchor pockets. This structure shows how low affinity peptides can be utilised in the design of novel peptide based tumour vaccines. The crystal structure of a second non-standard peptide complex (YEA9) at 1.5Å resolution demonstrates how YEA9 peptide can bind with surprisingly high affinity through insertion of alternative long non-canonical anchors into the B and E pockets. The use of alternative pockets represents a new mode of high affinity peptide binding, that should be considered when predicting high affinity epitopes for MHC class I. The molecular interactions elucidated in these non-canonical low and high affinity peptide MHC complexes should help uncover additional immunogenic peptides from primary protein sequences and aid in the design of alternative approaches for vaccines.