

The pairing of VL and VH domains in the Fab fragment of the antibody is outside the range of structures observed in other studies on uncomplexed Fab fragments. We interpret this observation to imply that antigen can induce a fit in the combining site of an antibody by a sliding of VL and VH domains at their interface, generating shifts in the position of the complementarity determining residues of up to 4Å.

Studies on a complex of neuraminidase with a second Fab fragment are well advanced and should further address the question of conformational changes in antigen-antibody interactions.

constrained-restrained crystallographic refinement (CORELS). The current R-factor is 37.2% for 8592 reflections. The resulting 2Fo-Fc map was of sufficient quality to permit a preliminary visualization of the inhibitor bound to the pepsin active site. Several putative differences were observed between the conformations of native and inhibited enzyme, including about a 1.5Å rms main chain movement of the flap residues (75-77) downward, towards the inhibitor. Probable interactions between pepsin and A63218 included a hydrogen bond between one of the key active site carboxylates, asp32, and the 3-OH of the inhibitor. Further refinement of both the apoenzyme and the complex crystal structures should elucidate the bioactive conformation of A63218 as well as the detailed intermolecular contacts and any additional structural changes for the inhibited enzyme.

02.4-6 THE 2.5Å CRYSTAL STRUCTURE OF A POTENT HUMAN RENIN INHIBITOR(A63218) BOUND TO PORCINE PEPSIN. J. Erickson, C. Abad-Zapatero, T.J. Rydel, and J. Luly, Pharmaceutical Discovery Division, Abbott Laboratories, USA.

Human renin is an aspartyl protease that is responsible for the humoral conversion of angiotensinogen to angiotensin I. This process is the first, and rate-limiting, step in the production of the peptide hormone angiotensin II, which exerts a powerful effect on both blood pressure and electrolyte balance. Thus, renin has been the target for the synthesis of a novel class of anti-hypertensive peptidomimetics. A number of potent(sub-nanomolar) renin inhibitors were found to also inhibit porcine pepsin, an aspartyl protease which exhibits nearly 40% sequence homology to human renin. In our attempts to design effective active site blockers for renin and to rationalize existing structure-activity data for Abbott peptidomimetics, several of these inhibitors were co-crystallized with pepsin at pH 2.0 in 20% ethanol. The crystal structure of the (2S,3R,4S)-2-(Etoc-p-I-phe-leu-amino)-1-cyclohexyl-3,4-dihydroxy-6-methyl-heptane(A63218) compound complexed with pepsin was solved at 2.5Å resolution using the partially-refined (R=33%, 10.0-3.0Å data) crystal structure of porcine pepsin in 20% ethanol (Andreeva, et al.,1984; Abad-Zapatero, et al., in preparation). The complex was crystallized in space group P2₁2₁2₁, with cell constants a=123.9Å, b=64.9Å, c=36.2Å, and with one complex in the asymmetric unit. The position and orientation of pepsin in the orthorhombic crystal cell were deduced from cross-rotation function searches and from packing considerations based on a comparison with the monoclinic pepsin crystal. After a six-parameter, rigid body R-factor minimization, the enzyme portion of the complex was refined against 10.0-2.5Å data using the method of

02.4-7 STRUCTURAL STUDIES ON THE LENS β , γ CRYSTALLINS. By B.Bax, M.Bibby, T.Blundell, H.Driessen, P.Lindley, L.Miller, D.Moss, S.Mylvaganam, S.Najmudin, C.Slingsby, H.White, Department of Crystallography, Birkbeck College, University of London, England.

The monomeric γ -crystallins and the oligomeric β -crystallins are thought to have evolved from a single ancestral gene. These two families of eye lens proteins account for a large proportion of protein in the mammalian lens. A high concentration of protein in the lens is necessary to maintain a high refractive index. We are studying the supramolecular organization of the lens by studying both the monomeric γ -crystallins and the oligomeric β -crystallins. A high resolution (1.5Å) study of bovine γ II crystallin, shows details of protein water interactions. Lower resolution studies of γ IIIb (2.6Å) and γ IVa (2.3Å) show subtle differences between these highly homologous structures (homology about 80%). We have determined the structure of bovine γ IVa using molecular replacement. The study of intermolecular contacts in γ II, γ IIIb and γ IVa crystals gives useful information about possible intermolecular contacts in the lens. Both bovine γ IIIb and β B2 form crystals showing pseudo-symmetry. The structure determination of β B2 at 3.4Å, using M.I.R., yields information about the quaternary interactions in the β -crystallin aggregates. β B2 crystallises with two dimers in the asymmetric unit (Mr 92kDa). Problems in structure determination have been encountered due to poorly diffracting crystals and pseudosymmetry. Progress is being made with a new tetrameric methane derivative. Model building studies have been carried out on the β -crystallins, based on their homology with the γ -crystallins (about 30%). These have revealed highly conserved surface regions on some orthologous β -crystallins from different species.