Complete Crystal Structure of Monocyte Chemotactic Protein-2, a CC Chemokine that Interacts with Multiple Receptors

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Introduction: Monocyte chemotactic protein 2 (MCP-2) is a CC chemokine that utilizes multiple cellular receptors to attract and activate human leukocytes. MCP-2 is a potent inhibitor of HIV-1 by virtue of its high-affinity binding to the receptor CCR5, one of the major co receptors for HIV-1. Although a few structures of CC chemokines have been reported, none of these was determined with the N-terminal pyroglutamic acid residue (pGlu1) and a complete C-terminus. pGlu1 is essential for the chemotactic activity of MCP-2. Recombinant MCP-2 has Gln1 at the N terminus, 12-15% of which cyclizes automatically and forms pGlu1. The chemotactic activity of such MCP-2 mixture, which contains 12-15% pGlu1- and 85-88% Gln1-form protein, is ~10 times lower when compared with that of fully cyclized MCP-2 preparation. Therefore, this chemokine is practically inactive without pGlu1.

Methods and Materials: Single crystal X-ray diffraction.

Results: We have determined the complete crystal structure of MCP-2 that contains both pGlu1 and an intact C-terminus. With the existence of pGlu1, the conformation of the N terminus allows two additional interactions between the two subunits of MCP-2 dimer: a hydrogen bond between pGlu1 and Asn17 and a salt bridge between Asp3 and Arg18. Consequently, both pGlu1 are anchored and buried, and thereby, both N-terminal regions are protected against protease degradation. We have also observed not previously reported extended helical nature of the C terminal region, which covers residues 58-74.

Conclusions: Functionally, pGlu1 is essential for the chemotactic activity of MCP-2. Structurally, pGlu1 of MCP-2 is essential to the conformation of the N terminus of MCP-2.

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