



Expression, Purification and Structural Analysis of Human IL-18 Binding Protein: A Potent Therapeutic Molecule for Allergy

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Background: While interleukin-18 (IL-18) plays an important role in the innate and adaptive immune responses, it can also cause severe allergic inflammatory reactions. Thus it is a molecule currently being targeted for therapy. The natural intrinsic inhibitor of IL-18 receptor activation, IL-18 binding protein (IL-18BP), shows a great potential for the treatment of allergy.

Methods: Expression and purification of recombinant human IL-18BP (rhIL-18BP) were performed using the baculovirus system to develop a therapeutic molecule for the treatment of IL-18-related diseases and to investigate the structural basis of its inhibitory mechanism.

Results: Purified rhIL-18BP potently inhibited the production of interferon-gamma by peripheral blood mononuclear cells in the presence of lipopolysaccharide and by human myelomonocytic KG-1 cells in the presence of IL-18 (IC₅₀ = 0.4 nM). Surface plasmon resonance showed a high affinity (K_d = 0.46 nM) for rhIL-18BP in binding hIL-18. Structural analysis indicated that the stoichiometry between IL-18 and IL-18BP is 1 : 1 in solution and the model structure of the complex suggests that the key residues on IL-18 (L5, K53, S55) and the estimated key residues on IL-18BP (F93, Y97, F104) could have interactions. The structural mechanism of IL-18BP inhibition might be a competition for Site 2 on rIL-18 so that IL-18BP can prevent IL-18 receptor alpha from binding to Site 2 and inhibit IL-18 receptor activation.

Conclusions: IL-18BP has unique features with respect to its structure, binding mode and inhibitory mechanism. It is a molecule that has a great potential for the therapy of allergy.

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