Mol Immunol. 1996 May-Jun;33(7-8):649-58.

# Generation and characterization of a human monoclonal autoantibody that acts as a high affinity interleukin-1 alpha specific inhibitor.

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## Abstract

Interleukin-1 (IL-1) defines two polypeptides, IL-1 alpha and IL-1 beta, that possess a wide spectrum of biological effects. Two natural antagonists of IL-1 action have been characterized: the IL-1 receptor antagonist (IL-1Ra) and a soluble form of the type II IL-1 receptor. Neutralizing autoantibodies to IL-1 alpha have also been detected in sera of healthy individuals and patients with autoimmune or inflammatory diseases. To characterize such antibodies molecularly, we attempted to generate B cell clones producing anti-IL-1 alpha human monoclonal antibody (HuMAb) by combining Epstein-Barr virus-immortalization and CD40-activation of B lymphocytes from individuals with circulating anti-IL-1 alpha. We describe herein the generation and properties of a natural IgG4/kappa anti-IL-1 alpha monoclonal autoantibody, HuMAb X3, that bound specifically to human IL-1 alpha, but not to IL-1 beta and IL-1Ra, with a high affinity (Kd = 1.2 x 10(-10)M). HuMAb X3 inhibited IL-1 alpha binding to IL-1 receptors and neutralized biological activities of both recombinant and natural forms of IL-1 alpha. A recombinant form of HuMAb X3 was found to display identical specific IL-1 alpha antagonism. The presence of somatic mutations within X3 variable regions suggests an antigen-driven affinity maturation. This study extends the demonstration of the presence of high affinity neutralizing anti-IL-1 alpha autoantibodies that can function as a third type of IL-1 antagonist.

PMID:
8760277
[PubMed - indexed for MEDLINE]